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Vitamin D for the management of asthma

Adrian R Martineau¹, Christopher J Cates², Mitsuyoshi Urashima³, Megan Jensen⁴, Alex P Griffiths¹, Ulugbek Nurmatov⁵, Aziz Sheikh⁶, Chris J Griffiths¹

¹Centre for Primary Care and Public Health and Asthma UK Centre for Applied Research, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK. ²Population Health Research Institute, St George's, University of London, London, UK. ³Division of Molecular Epidemiology, Jikei University School of Medicine, Tokyo, Japan. ⁴Centre for Asthma and Respiratory Diseases, University of Newcastle, Newcastle, Australia. ⁵Division of Population Medicine, School of Medicine, Cardiff University, Cardiff, UK. ⁶Allergy & Respiratory Research Group and Asthma UK Centre for Applied Research, Centre for Medical Informatics, Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, UK

Contact address: Adrian R Martineau, Centre for Primary Care and Public Health and Asthma UK Centre for Applied Research, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK. a.martineau@qmul.ac.uk.

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ABSTRACT

Background

Several clinical trials of vitamin D to prevent asthma exacerbation and improve asthma control have been conducted in children and adults, but a meta-analysis restricted to double-blind, randomised, placebo-controlled trials of this intervention is lacking.

Objectives

To evaluate the efficacy of administration of vitamin D and its hydroxylated metabolites in reducing the risk of severe asthma exacerbations (defined as those requiring treatment with systemic corticosteroids) and improving asthma symptom control.

Search methods

We searched the Cochrane Airways Group Trial Register and reference lists of articles. We contacted the authors of studies in order to identify additional trials. Date of last search: January 2016.

Selection criteria

Double-blind, randomised, placebo-controlled trials of vitamin D in children and adults with asthma evaluating exacerbation risk or asthma symptom control or both.

Data collection and analysis

Two review authors independently applied study inclusion criteria, extracted the data, and assessed risk of bias. We obtained missing data from the authors where possible. We reported results with 95% confidence intervals (CIs).

Main results

We included seven trials involving a total of 435 children and two trials involving a total of 658 adults in the primary analysis. Of these, one trial involving 22 children and two trials involving 658 adults contributed to the analysis of the rate of exacerbations requiring systemic corticosteroids. Duration of trials ranged from four to 12 months, and the majority of participants had mild to moderate asthma. Administration of vitamin D reduced the rate of exacerbations requiring systemic corticosteroids (rate ratio 0.63, 95% CI 0.45 to 0.88; 680 participants; 3 studies; high-quality evidence), and decreased the risk of having at least one exacerbation requiring an emergency department visit or hospitalisation or both (odds ratio (OR) 0.39, 95% CI 0.19 to 0.78; number needed to treat for an additional beneficial outcome, 27; 963 participants; 7 studies; high-quality evidence). There was no effect of vitamin D on % predicted forced expiratory volume in one second (mean difference (MD) 0.48, 95% CI -0.93 to 1.89; 387 participants; 4 studies; high-quality evidence) or Asthma Control Test scores (MD -0.08, 95% CI -0.70 to 0.54; 713 participants; 3 studies; high-quality evidence). Administration of vitamin D did not influence the risk of serious adverse events (OR 1.01, 95% CI 0.54 to 1.89; 879 participants; 5 studies; moderate-quality evidence). One trial comparing low-dose versus high-dose vitamin D reported two episodes of hypercalciuria, one in each study arm. No other study reported any adverse event potentially attributable to administration of vitamin D. No participant in any included trial suffered a fatal asthma exacerbation. We did not perform a subgroup analysis to determine whether the effect of vitamin D on risk of severe exacerbation was modified by baseline vitamin D status, due to unavailability of suitably disaggregated data. We assessed two trials as being at high risk of bias in at least one domain; neither trial contributed data to the analysis of the outcomes reported above.

Authors' conclusions

Meta-analysis of a modest number of trials in people with predominantly mild to moderate asthma suggests that vitamin D is likely to reduce both the risk of severe asthma exacerbation and healthcare use. It is as yet unclear whether these effects are confined to people with lower baseline vitamin D status; further research, including individual patient data meta-analysis of existing datasets, is needed to clarify this issue. Children and people with frequent severe asthma exacerbations were under-represented; additional primary trials are needed to establish whether vitamin D can reduce the risk of severe asthma exacerbation in these groups.

PLAIN LANGUAGE SUMMARY

Vitamin D to prevent asthma attacks

Review question

Does vitamin D prevent asthma attacks or improve control of asthma symptoms or both?

Background

Low blood levels of vitamin D (the 'sunshine vitamin') have been linked to an increased risk of asthma attacks in children and adults with asthma. Several clinical trials have been conducted to test whether vitamin D might prevent asthma attacks and improve control of asthma symptoms in children and adults, but results from studies with the most scientifically sound designs have not previously been evaluated as a group.

Included studies

We included seven trials involving 435 children and two trials involving 658 adults in the review from searches run up to January 2016. Of these, one trial involving 22 children and two trials involving 658 adults contributed to the analysis of the rate of severe asthma attacks. Study duration ranged from four to 12 months, and the majority of those taking part had mild or moderate asthma. All of the studies compared vitamin D with placebo.

Key results

People given vitamin D experienced fewer asthma attacks needing treatment with oral steroids. The average number of attacks per person per year went down from 0.44 to 0.28 with vitamin D (high-quality evidence). Vitamin D reduced the risk of attending hospital with an acute asthma attack from 6 per 100 to around 3 per 100 (high-quality evidence).

Vitamin D had little or no effect on lung function or day-to-day asthma symptoms (high-quality evidence). We found that vitamin D did not increase the risk of serious adverse events at the doses that were tested (moderate-quality evidence).

We based all of these findings on studies judged to be of high quality.

Conclusion

Vitamin D is likely to offer protection against severe asthma attacks. Further trials focusing on children and people who experience frequent severe asthma attacks are needed before definitive clinical recommendations can be made.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Vitamin D versus placebo for the management of asthma (all studies)						
Patient or population: children and adults with predominantly mild to moderate asthma Setting: primary and secondary care Intervention: vitamin D ₃ administered orally over study duration of 4 to 12 months Comparison: placebo						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with vitamin D				
Rate ratio, exacerbations requiring systemic corticosteroids assessed with: number of events per participant per year. Follow-up: 6 to 12 months	Study population		RR 0.63 (0.45 to 0.88)	680 (3 RCTs)	⊕⊕⊕⊕ HIGH	Evidence based primarily on adults with mild to moderate asthma
	0.44 events per person per year ¹	0.28 events per person per year (0.20 to 0.39)				
People with 1 or more exacerbations requiring ED visit or hospitalisation or both. Follow-up: 6 to 12 months	Study population		OR 0.39 (0.19 to 0.78)	963 (7 RCTs)	⊕⊕⊕⊕ HIGH	Evidence based primarily on children and adults with mild to moderate asthma
	63 per 1000	25 per 1000 (13 to 50)				
FEV1, % predicted. Follow-up: 6 to 12 months	The mean FEV1, % predicted was 85.62%	The mean FEV1, % predicted in the intervention group was 0.48% more (0.93 fewer to 1.89 more)	-	387 (4 RCTs)	⊕⊕⊕⊕ ² HIGH	Evidence based primarily on children and adults with mild to moderate asthma

ACT/C-ACT score. Follow-up: 6 to 12 months	The mean ACT/C-ACT score was 20 points	The mean ACT/C-ACT score in the intervention group was 0.08 points fewer (0.7 fewer to 0.54 more)	-	713 (3 RCTs)	⊕⊕⊕⊕ ² HIGH	Evidence based primarily on adults with mild to moderate asthma
People with fatal asthma exacerbation. Follow-up: 6 to 12 months	Study population		Not estimable	963 (7 RCTs)	⊕⊕⊕○ ³ LOW	No fatal asthma exacerbations occurred in included studies
	0 per 1000	0 per 1000 (0 to 0)				
People with 1 or more serious adverse event due to any cause. Follow-up: 6 to 12 months	Study population		OR 1.01 (0.54 to 1.89)	879 (5 RCTs)	⊕⊕⊕○ ⁴ MODERATE	Evidence based primarily on children and adults with mild to moderate asthma
	48 per 1000	49 per 1000 (27 to 87)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ACT, Asthma Control Test; C-ACT, Childhood Asthma Control Test; CI, confidence interval; ED, emergency department; FEV1, forced expiratory volume in one second; OR, odds ratio; RCT, randomised controlled trial; RR, rate ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

¹The event rate in participants randomised to placebo was estimated by calculating the weighted mean of event rates reported in placebo arms of included studies.

²Despite null effects of the intervention on these outcomes, we are confident that the true effect lies close to the estimates, as 95% confidence intervals for these estimates are very narrow.

³Downgraded two levels due to imprecision (no events occurred in included studies).

⁴Downgraded one level due to imprecision (wide confidence intervals).

BACKGROUND

Description of the condition

Asthma is a chronic inflammatory condition of the airways, characterised by recurrent attacks of breathlessness, wheezing, cough, and chest tightness, commonly termed 'exacerbations'. The prevalence of asthma varies widely between countries. In children, the prevalence of severe asthma symptoms ranges from 0% (India) to 20.3% (Costa Rica) (Lai 2009); in adults, the prevalence of doctor-diagnosed asthma ranges from 0.2% (China) to 21.0% (Australia) (To 2012). Exacerbations represent the major cause of morbidity and mortality in people with asthma (Johnston 2006). Asthma exacerbations are commonly classified as severe when they require treatment with systemic corticosteroids and/or when they result in emergency department attendance, hospitalisation, or death (Reddel 2009). Common precipitants of asthma exacerbation include acute respiratory infections and exposure to allergens and particulates (Singh 2006).

Description of the intervention

Vitamin D is a fat-soluble micronutrient that has two 'parent' forms: cholecalciferol (vitamin D₃) and ergocalciferol (vitamin D₂). Cholecalciferol is synthesised in human skin from its precursor molecule 7-dehydrocholesterol on exposure to ultraviolet B (UVB) radiation in sunlight; it may also be ingested, either in the diet (primarily from eating oily fish or vitamin D-fortified foods) or as vitamin D supplements. Ergocalciferol is the plant and fungal form of the vitamin, which may be ingested in the diet (primarily by eating fungi) or as vitamin D supplements. In situations where cutaneous exposure to UVB radiation of appropriate intensity is limited (for example during winter at latitudes above 34°N or below 34°S, or in settings where people do not regularly expose their skin to sunlight), dietary sources of vitamin D or vitamin D supplements or both may be required to meet the body's vitamin D requirement (Holick 2007).

Following cutaneous synthesis or ingestion, both forms of parent vitamin D undergo metabolism to form 25-hydroxyvitamin D (25(OH)D), the major circulating vitamin D metabolite whose serum concentration indicates vitamin D status. 25-hydroxylation may occur in the liver and in extra-hepatic tissues, including leucocytes (Holick 2007). Serum 25(OH)D concentrations less than 50 nmol/L are widely accepted to indicate vitamin D deficiency; concentrations less than 25 nmol/L represent profound deficiency. Concentrations of 50 to 74 nmol/L may represent a milder state of inadequate vitamin D status, commonly termed 'vitamin D insufficiency'. 25(OH)D undergoes a second hydroxylation step at the 1-alpha position to form the active vitamin D metabolite 1,25-dihydroxyvitamin D (1,25(OH)₂D), the steroid hormone

and active vitamin D metabolite that mediates the biological actions of vitamin D by binding the vitamin D receptor to regulate gene expression (Holick 2007). This 1-alpha hydroxylation step is catalysed by the enzyme CYP27B1, which is expressed in many tissues including the kidney, leucocytes, and pulmonary epithelium; expression of CYP27B1 in leucocytes and pulmonary epithelium is up-regulated in response to infection and inflammation.

This review included studies evaluating the effects of administration, by any route and at any dose, of vitamin D₃, vitamin D₂, 25(OH)D, or 1,25(OH)₂D. Vitamin D₃, vitamin D₂, and 25(OH)D are usually administered orally; the 'parent compounds' vitamin D₃ and vitamin D₂ may also be given intramuscularly. Intramuscular administration of a bolus dose of vitamin D induces a slower increase and a lower peak in serum 25(OH)D than oral administration of the same dose (Romagnoli 2008), consequently this route of administration is not widely employed in clinical trials of vitamin D. The functional in vivo half-life of 25(OH)D in the circulation is one to two months; accordingly, it takes at least three months to attain steady-state concentrations of 25(OH)D in response to daily administration of vitamin D (Heaney 2003). Due to the relatively long half-life of 25(OH)D, parent vitamin D and 25(OH)D may be administered intermittently as well as daily; weekly and monthly dosing regimens are often employed, and more widely spaced dosing regimens are also sometimes used. However, dosing less frequently than monthly results in large non-physiological fluctuations in serum 25(OH)D concentration, which may cause undesirable effects (Hollis 2013; Martineau 2012; Vieth 2009). The influence of dosing interval on biological responses to administration of vitamin D is an area of active research in the field.

How the intervention might work

About 1 billion people worldwide are estimated to have 25(OH)D levels of less than 75 nmol/L (Holick 2007). Inadequate vitamin D status has been reported to be common among people with asthma in a variety of settings. Cross-sectional, Brehm 2012, and cohort, Brehm 2010 and Confino-Cohen 2014, studies have demonstrated independent associations between inadequate vitamin D status and increased risk of exacerbations. Administration of vitamin D₃, vitamin D₂, or 25(OH)D results in increased circulating concentrations of 25(OH)D. This 25(OH)D acts as a substrate for CYP27B1 expressed in the kidney and multiple extra-renal tissues. Of particular relevance for asthma, CYP27B1 expression in the airway and leucocytes is induced during infection and inflammation, so that the active vitamin D metabolite 1,25(OH)₂D is synthesised locally in the lung. 1,25(OH)₂D ligates the vitamin D receptor (VDR) to induce antimicrobial activity (for example by induction of antimicrobial peptide expression), Greiller 2015 and Martineau 2007, and exert anti-inflammatory activity (for example by induction of the anti-inflammatory cytokine IL-10, suppression of proinflammatory tumour necrosis factor and inter-

feron- γ -inducible chemokines, and inhibition of lipopolysaccharide-induced synthesis of reactive oxygen species) (Coussens 2012; Lan 2014; Mann 2014). This combination of antimicrobial, antiviral, and anti-inflammatory activity might decrease the risk of exacerbations, which are often precipitated by respiratory infection and which are characterised by dysregulated pulmonary inflammation. Of particular relevance to asthma, 1,25(OH) $_2$ D has been shown to inhibit TH17 cytokine production and enhance responsiveness to inhaled corticosteroids for production of interleukin-10 *ex vivo* in people with asthma (Nanzer 2014; Xystrakis 2006). These findings raise the possibility that administration of vitamin D or 25(OH)D may therefore have a role in reducing exacerbation risk and improving symptom control in combination with inhaled corticosteroids, as well as independently. However, controversy exists regarding what serum 25(OH)D concentration, if any, is optimum for reducing the risk of asthma exacerbations.

Why it is important to do this review

There is considerable interest in the potential of administration of vitamin D to reduce exacerbation risk and improve asthma symptom control. Several published trials of vitamin D in children with asthma have reported statistically significant reductions in exacerbation rates among children randomised to the intervention arm (Majak 2011; Urashima 2010; Yadav 2014), two trials in adults have also reported non-statistically significant trends towards reduced exacerbation rates in their intervention arms (Castro 2014; Martineau 2015). Meta-analysis of these trials has the potential to increase statistical power to detect effects of administering vitamin D on exacerbation risk. However, definitions of severe exacerbation differ between trials, and published meta-analyses in the field have utilised the variable definitions reported in primary publications rather than adopting a unified definition for this outcome across studies (Luo 2015; Riverin 2015; Xiao 2015). These meta-analyses also included some non-placebo-controlled trials (Baris 2014; Darabi 2013), as well as trials of relatively short duration (less than 12 weeks) (De Groot 2015; Schou 2003). We therefore conducted a meta-analysis that was restricted to double-blind, placebo-controlled trials of at least 12 weeks' duration to determine the effect of vitamin D on the primary outcome of exacerbation treated with systemic corticosteroids.

OBJECTIVES

To evaluate the efficacy of administration of vitamin D and its hydroxylated metabolites in reducing the risk of severe asthma exacerbations (defined as those requiring treatment with systemic corticosteroids) and improving asthma symptom control.

METHODS

Criteria for considering studies for this review

Types of studies

We reviewed double-blind, randomised, placebo-controlled trials of at least 12 weeks' duration. We did not include studies focusing only on bone outcomes, which we considered to provide very limited insights into asthma morbidity. We included studies reported as full text and unpublished data. Where eligible studies were published as abstracts only, we contacted the authors to request the full text of the trial report; where full text was unavailable, we listed such studies as 'ongoing'.

Types of participants

We included children and adults with a clinical diagnosis of asthma, based on the presence of characteristic symptoms and signs (wheeze, shortness of breath, chest tightness, or cough) and variable airflow obstruction. We imposed no restrictions regarding disease severity, baseline vitamin D status, or duration of treatment with asthma medication.

Types of interventions

The review was open to studies in which vitamin D $_3$, vitamin D $_2$, 25(OH)D, or 1,25(OH) $_2$ D was administered at any dose.

Types of outcome measures

Primary outcomes

1. Incidence of severe asthma exacerbations, defined as those requiring treatment with systemic corticosteroids

Secondary outcomes

1. Incidence of asthma exacerbations precipitating an emergency department visit or requiring hospital admission or both
2. End-study Asthma Control Test (ACT) score
3. End-study % predicted forced expiratory volume in one second (FEV1)
4. Incidence of any severe adverse event, irrespective of causation
5. Incidence of fatal asthma exacerbation
6. Incidence of asthma exacerbation as defined in the study protocol
7. End-study % eosinophils in induced sputum or bronchoalveolar lavage
8. End-study peak expiratory flow rate

9. Incidence of adverse reactions attributed to administration of vitamin D or its metabolites
10. Proportion of participants withdrawing from the trial

We would have meta-analysed the following secondary outcomes had sufficient data been available.

1. Time off school or work due to asthma symptoms
2. Beta2-agonist inhaler use
3. End-study asthma quality of life as judged by use of a validated instrument
4. End-study fractional exhaled nitric oxide concentration
5. End-study airway reactivity
6. Costs from the perspective of healthcare providers

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Group's Specialised Register (CAGR), which is maintained by the information specialist for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED, and PsycINFO, and handsearching of respiratory journals and meeting abstracts (please see Appendix 1 for further details). We searched all records in the CAGR using the search strategy in Appendix 2. We also conducted searches of ClinicalTrials.gov (www.ClinicalTrials.gov), the World Health Organization trials portal (www.who.int/ictrp/en/), the ISRCTN registry (www.isrctn.com/), the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au/), and the UMIN Clinical Trials Registry (www.umin.ac.jp/ctr/). We searched all databases from their inception to 6 January 2016, and imposed no restriction on language of publication.

Searching other resources

We checked reference lists of all primary studies and review articles for additional references. We searched relevant manufacturers' websites for trial information.

We searched for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed), but did not find any. We also contacted a panel of international experts for additional references and information on trials in progress.

Data collection and analysis

Selection of studies

Two people (Adrian R Martineau (ARM) and either Christopher J Cates (CJC) or Andrea Takeda (AT)) independently screened for inclusion the titles and abstracts of all the potentially relevant studies identified as a result of the search, coding them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We then retrieved the full-text study reports/publication, and two people (ARM and either CJC or AT) independently screened the full text, identifying studies for inclusion and identifying and recording reasons for exclusion of the ineligible studies. Any disagreements were resolved through discussion or by consultation with other members of the review team (Christopher J Griffiths (CJG) and Aziz Sheikh (AS)) or both. We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

We used a data collection form for study characteristics and outcome data which was piloted on at least one study in the review. Two review authors (ARM and one of CJC, CJG, and Alex P Griffiths (APG)) extracted study characteristics from each included study. We extracted the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: number, mean age, age range, gender, body mass index, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (ARM and one of CJC, CJG, and APG) independently extracted outcome data from each included study. If outcome data were not reported in a usable way, we noted this in the 'Characteristics of included studies' table. We resolved disagreements by consensus or by involving a third person (CJG or AS). One review author (ARM) transferred data into the RevMan 2015 file. We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (CJC) checked study characteristics for accuracy against the trial reports.

Assessment of risk of bias in included studies

The 'Risk of bias' assessment for the study authored by ARM and CJG, Martineau 2015, was performed by Ulugbek Nurmatov

(UN) and CJC. For all other studies, two review authors (ARM and one of CJC and APG) independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or by involving another review author (AS). We assessed the risk of bias according to the following domains.

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Other biases, including study size

We graded each potential source of bias as high, low, or unclear and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We summarised the 'Risk of bias' judgements across different studies for each of the domains listed. Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table. When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to a published protocol (Martineau 2015b), and have reported any deviations from it in the [Differences between protocol and review](#) section.

Measures of treatment effect

We analysed event rates as rate ratios (RR), dichotomous data as odds ratios (OR), and times to first event as hazard ratios (HR). We analysed other continuous outcome measures as mean difference (MD) or standardised mean difference (SMD). We used generic inverse variance meta-analysis where adjusted measures of treatment effect from individual trials were included. We entered data presented as a scale with a consistent direction of effect. For analyses of outcomes in which no events occurred in some studies, we also calculated risk differences (RD). We undertook meta-analyses only where this was meaningful, that is if the treatments, participants, and the underlying clinical question were similar enough for pooling to make sense.

Where multiple trial arms were reported in a single trial, we included only the relevant arms. If two comparisons (for example drug A versus placebo and drug B versus placebo) had been combined in the same meta-analysis, we would have halved the control group to avoid double-counting.

For outcomes measured at different time points, we included the longest time point after randomisation.

Unit of analysis issues

If data had been expressed in unconventional units of analysis, we would have converted them to conventional units, liaising with the authors where required.

Dealing with missing data

We contacted investigators or study sponsors in order to verify key study characteristics and to obtain missing numerical outcome data where possible. We asked all investigators to provide data relating to the incidence of fatal asthma exacerbations and exacerbations requiring treatment with systemic corticosteroids or emergency department attendance/hospitalisation or both where these were not reported in the manuscript or abstract.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. Where we identified substantial heterogeneity (I^2 greater than 40%), we assessed the value of exploring possible causes by using a prespecified subgroup analysis. However, limitations of the available data (for example where data for participants within different subgroups could not be disaggregated, or where numbers of participants or events or both within a subgroup were small) precluded the conduct of such subgroup analyses.

Assessment of reporting biases

Had we been able to pool more than 10 trials, we would have created and examined a funnel plot to explore possible small-study biases.

Data synthesis

Given significant heterogeneity between studies, we used a random-effects model for the primary analysis. We performed sensitivity analyses using fixed-effect models for outcomes where the two models yielded different results. We analysed all data by intention-to-treat. We synthesised event rates as RRs, dichotomous data as ORs, and times to first event as HRs. We synthesised other continuous outcome measures as MD or SMD. We calculated the number needed to treat for an additional beneficial outcome (NNTB) using the Visual Rx NNT calculator (www.nntonline.net/visualrx/) where meta-analysis of dichotomous outcomes revealed a statistically significant beneficial effect of allocation to vitamin D. We would have similarly calculated the number needed to treat for an additional harmful outcome (NNTH) if meta-analysis of dichotomous outcomes had revealed statistically significant harmful effects of vitamin D. We used means and standard deviations (SDs) when available. Where data were not reported we approached the study authors. We would have extracted values from graphs had study authors not responded.

'Summary of findings' table

We created a 'Summary of findings' table using the following outcomes: incidence of asthma exacerbation treated with systemic corticosteroids; incidence of asthma exacerbation requiring emergency department attendance or hospitalisation for asthma or both; end-study % predicted FEV1; end-study ACT score; incidence of fatal asthma exacerbation; and incidence of serious adverse events due to any cause. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the body of evidence as it related to the studies which contributed data to the meta-analyses for the prespecified outcomes. Where data from primary studies conducted by review authors contributed to a given outcome, the quality of the evidence was assessed by review authors who were not involved with those primary studies (CJC and AS). We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions*, [Higgins 2011](#), using [GRADEpro GDT 2014](#) software. We justified all decisions to down- or upgrade the quality of studies using footnotes where necessary.

Subgroup analysis and investigation of heterogeneity

We prespecified that we would carry out the following subgroup analyses for the outcome of exacerbation treated with systemic corticosteroids ([Martineau 2015b](#)).

1. Baseline vitamin D status (e.g. serum 25(OH)D < 50 nmol/L versus \geq 50 nmol/L).
2. Age (e.g. children aged < 5 years versus 5 to 16 years versus adults).
3. Severity of asthma and concomitant asthma treatment being taken (e.g. taking versus not taking inhaled corticosteroids, taking versus not taking leukotriene receptor antagonists).
4. The dose (e.g. daily equivalent of < 400 IU versus 400 to 2000 IU versus > 2000 IU) and form of vitamin D administered (e.g. cholecalciferol versus calcitriol).

5. The frequency of administration (e.g. daily versus intermittent bolus doses).

6. Genetic variation in pathways of vitamin D metabolism, transport, and signalling (e.g. GC 2/2 versus 2/1 versus 1/1 genotype for the GC polymorphism of the vitamin D binding protein).

7. Body mass index (e.g. < 25 kg/m² versus \geq 25 kg/m²).

However, limitations of the available data (for example where data for participants within different subgroups could not be disaggregated, or where numbers of participants or events or both within a subgroup were small) precluded the conduct of such subgroup analyses.

Had we conducted these subgroup analyses, we would have used the formal test for subgroup interactions in [RevMan 2015](#).

Sensitivity analysis

We carried out the following sensitivity analyses.

1. Exclusion of publications assessed as being at high risk of bias in one or more of the following domains: sequence generation, allocation concealment, blinding, completeness of outcome data, or selective outcome reporting.
2. Analyses using fixed-effect models were performed for outcomes where such models yielded results different from those generated by random-effects models ([Table 1](#)).

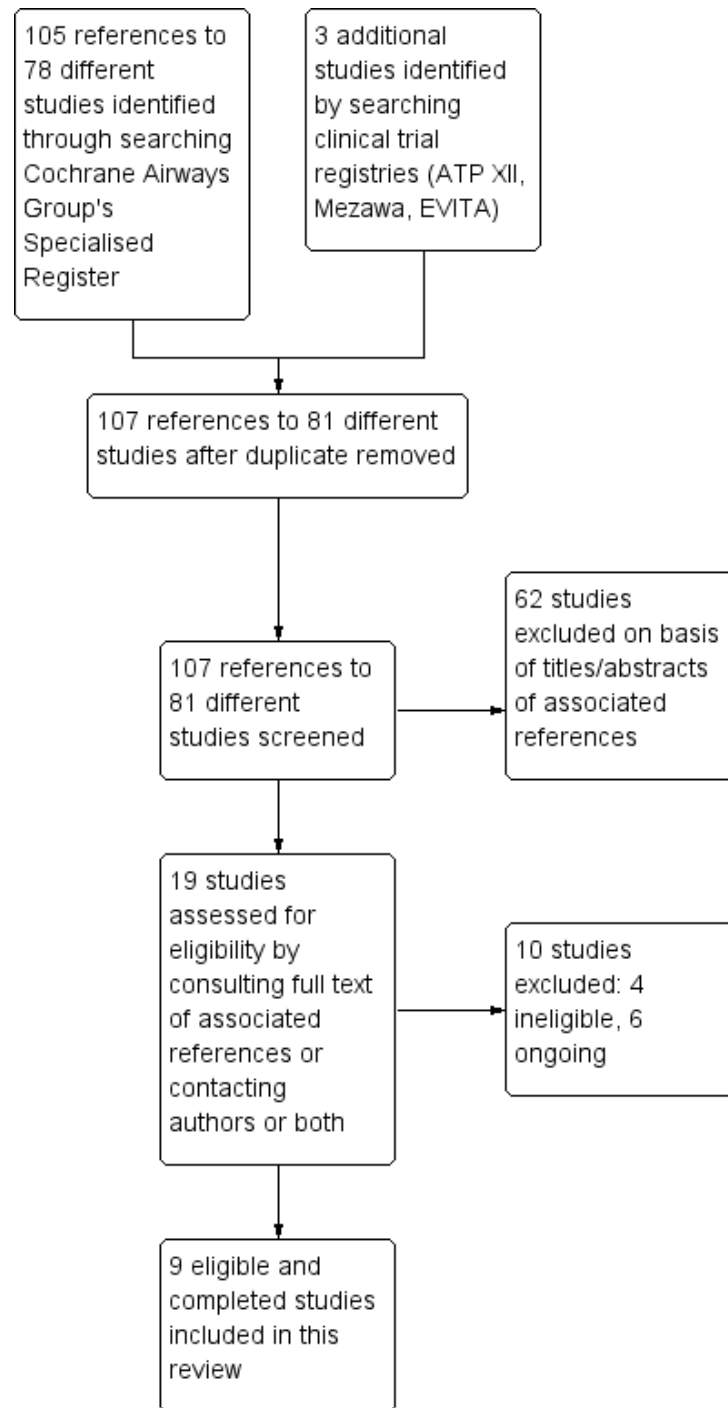
RESULTS

Description of studies

Results of the search

See [Figure 1](#) for full details.

Figure 1. Study flow diagram.



We identified a total of 105 references to 78 different studies by searching the CAGR and an additional three studies by searching clinical trial registries. After removing one duplicate reference, we screened 107 references to 81 different studies for eligibility. We excluded 62 studies on the basis of the titles or the abstracts or both of the associated references. We assessed the remaining 19 studies for eligibility by consulting the full text of associated references or contacting study authors or both; we then excluded 10 more studies, four of which did not meet eligibility criteria for inclusion and six of which we classified as ongoing. We have presented the reasons for excluding potentially relevant studies in the [Characteristics of excluded studies](#) table.

Included studies

See [Characteristics of included studies](#) for full details. Nine completed studies including a total of 1093 participants with asthma met the inclusion criteria for this review (Castro 2014; Jensen 2016; Lewis 2012; Majak 2009; Majak 2011; Martineau 2015; Tachimoto 2016; Urashima 2010; Yadav 2014).

Study design

All included studies were double-blind randomised controlled trials with a parallel-group design, open to male and female participants of any ethnic background; five were conducted at a single centre (Jensen 2016; Lewis 2012; Majak 2009; Majak 2011; Yadav 2014), and four were multicentre studies (Castro 2014; Martineau 2015; Tachimoto 2016; Urashima 2010). All studies recruited in secondary care, and one study also recruited in primary care (Martineau 2015). Study duration ranged from four months, in Urashima 2010, to 12 months, in Lewis 2012, Majak 2009, and Martineau 2015. All trials were restricted to individuals with a physician diagnosis of asthma; two trials additionally based eligibility on evidence of reversible or variable airway obstruction (Castro 2014; Martineau 2015). Current treatment with inhaled corticosteroids was a requirement for three trials (Castro 2014; Majak 2009; Martineau 2015), and an exclusion criterion for one trial (Majak 2011); one trial excluded participants who had received oral corticosteroid therapy in the year prior to enrolment (Urashima 2010). All of the remaining trials included at least some participants who were taking inhaled corticosteroids.

Only one trial included baseline vitamin D status as an eligibility criterion (Castro 2014, which excluded people with baseline 25(OH)D concentration greater than or equal to 75 nmol/L), but six trials had exclusion criteria relating to maximum permitted pre-trial or concomitant supplemental vitamin D intake or both (Castro 2014; Jensen 2016; Majak 2009; Majak 2011; Martineau 2015; Tachimoto 2016).

Participants

Seven studies involved 435 children (Jensen 2016; Lewis 2012; Majak 2009; Majak 2011; Tachimoto 2016; Urashima 2010; Yadav 2014), and two studies involved 658 adults (Castro 2014; Martineau 2015). Participants were ethnically diverse, reflecting the broad range of geographic settings: Canada (Jensen 2016), India (Yadav 2014), Japan (Tachimoto 2016; Urashima 2010), Poland (Majak 2009; Majak 2011), the UK (Martineau 2015), and the USA (Castro 2014; Lewis 2012). The majority of participants had mild/moderate asthma, and a minority had severe asthma. Where measured, mean/median baseline serum 25(OH)D concentration ranged from 48 nmol/L, in Castro 2014, to 89 nmol/L, in Majak 2011; a small minority of participants had serum 25(OH)D concentrations in the profoundly deficient range (less than 25 nmol/L).

Intervention

All studies administered oral vitamin D₃ (cholecalciferol) to participants in the intervention arm. There was considerable heterogeneity in vitamin D dosage regimens employed. Four studies, Lewis 2012, Majak 2011, Tachimoto 2016, and Urashima 2010, used exclusively daily dosing regimens ranging from 500 IU/day, in Majak 2011, to 1200 IU/day, in Urashima 2010. Of the other studies, one used weekly dosing (Majak 2009), one used monthly dosing (Yadav 2014), one used two-monthly dosing (Martineau 2015), and two gave a bolus dose at the start of the study, followed by daily dosing (Castro 2014; Jensen 2016). One study administered low-dose vitamin D (400 IU/day) to participants in both the control arm and intervention arm; participants in the intervention arm of this study received an additional bolus of 100,000 IU vitamin D at the start of the study (Jensen 2016). For the six trials in which vitamin D was given daily (with or without additional bolus doses) (Castro 2014; Jensen 2016; Lewis 2012; Majak 2011; Tachimoto 2016; Urashima 2010), the median daily dose was 900 IU/day, ranging from 400 IU/day, in Jensen 2016, to 4000 IU/day, in Castro 2014. Where vitamin D status was assessed, the intervention resulted in an interarm difference in follow-up serum 25(OH)D concentration on at least one follow-up time point in four studies (Castro 2014; Jensen 2016; Martineau 2015; Tachimoto 2016), but not in three others (Lewis 2012; Majak 2009; Majak 2011).

Outcomes

Seven trials reported asthma exacerbation as an outcome measure (Castro 2014; Jensen 2016; Majak 2011; Martineau 2015; Tachimoto 2016; Urashima 2010; Yadav 2014). Definitions of exacerbation varied significantly between trials. Authors of seven

trials provided data on exacerbations requiring treatment with systemic corticosteroids for the purposes of this review ([Castro 2014](#); [Jensen 2016](#); [Majak 2009](#); [Majak 2011](#); [Martineau 2015](#); [Tachimoto 2016](#); [Urashima 2010](#)).

Excluded studies

See [Characteristics of excluded studies](#) for full details.

Risk of bias in included studies

An overview of 'Risk of bias' judgements is shown in [Figure 2](#).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Castro 2014	+	+	+	+	+	+	+
Jensen 2016	+	+	+	+	+	+	+
Lewis 2012	?	?	+	+	-	+	+
Majak 2009	+	+	+	+	+	+	+
Majak 2011	+	?	+	+	+	+	+
Martineau 2015	+	+	+	+	+	+	+
Tachimoto 2016	+	+	+	+	+	+	+
Urashima 2010	+	+	+	+	?	+	+
Yadav 2014	?	+	+	+	-	+	-

Allocation

Two studies did not report the method of sequence generation (Lewis 2012; Yadav 2014), and two studies did not report the method of allocation concealment (Lewis 2012; Majak 2011). We have therefore classified the risk of selection bias for these studies as 'unclear'. We assessed the risk of selection bias for the remaining studies as low.

Blinding

It appears that participants and study personnel, including those who administered the intervention, have been effectively blinded to allocation for all studies; accordingly, we assessed the risk of performance and detection bias as low for all studies.

Incomplete outcome data

One-third of participants in the study by Lewis et al were lost to follow-up (Lewis 2012); we have therefore assessed the risk of attrition bias as high for this study. The study by Yadav et al reports that 18 out of 100 participants were lost to follow-up, but follow-up data for 100 participants was presented for the final follow-up visit (Yadav 2014). This discrepancy led us to assess the risk of attrition bias as being high for this study. We assessed the study by Urashima et al as being at unclear risk of attrition bias (Urashima 2010); although rates of loss were comparable between arms for this trial as a whole (50 out of 217 intervention arm, 46 out of 213 control arm), they were not reported for the subgroup of participants with doctor-diagnosed asthma. We assessed the risk of attrition bias for the remaining studies as low.

Selective reporting

We found no evidence of selective reporting for any of the included studies, and have therefore assessed the risk of reporting bias as low for all studies.

Other potential sources of bias

In the study by Yadav et al (Yadav 2014), we noted a marked change in classification of asthma severity between the six-month time point and earlier time points. This suggested a high risk of misclassification bias operating at the final follow-up time point. We identified no other potential sources of bias for the remaining included trials.

Effects of interventions

See: [Summary of findings for the main comparison Vitamin D versus placebo for the management of asthma \(all studies\)](#)

See [Summary of findings for the main comparison](#).

Vitamin D versus placebo: all eligible trials

Nine trials with a total of 1093 participants (435 children and 658 adults) contributed to this comparison for at least one outcome. Three trials with a total of 680 participants (22 children and 658 adults) contributed to this comparison for analysis of the rate of exacerbations requiring systemic corticosteroids.

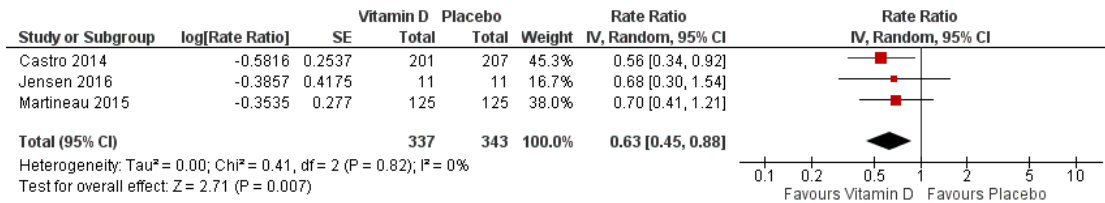
Primary outcome

Asthma exacerbation treated with systemic corticosteroids

Analyses including all participants

Administration of vitamin D was associated with a statistically significant reduction in the rate of asthma exacerbations treated with systemic corticosteroids (RR 0.63, 95% confidence interval (CI) 0.45 to 0.88; 680 participants; 3 studies; high-quality evidence; Analysis 1.1; [Figure 3](#)). We found weaker evidence to suggest a benefit of vitamin D for the outcomes of time to first such exacerbation (HR 0.69, 95% CI 0.48 to 1.00; 658 participants; 2 studies; moderate-quality evidence; Analysis 1.2) and proportion of participants experiencing one or more such exacerbation (OR 0.74, 95% CI 0.49 to 1.10; 933 participants; 7 studies; moderate-quality evidence; Analysis 1.3); 95% confidence intervals included or spanned 1.00 for these outcomes. Of note, trials conducted in adults contributed a disproportionate amount of data to these analyses (Castro 2014; Martineau 2015); severe exacerbations were only seen in two out of five trials that enrolled children (Jensen 2016; Tachimoto 2016), and the total numbers of such events were small. Also of note, only one child in the trial by Tachimoto et al experienced such an event (Tachimoto 2016), therefore RRs and HRs for this study could not be calculated. Time-to-event data for calculation of HRs were not available for the other paediatric trial that saw any such events (Jensen 2016).

Figure 3. Forest plot of comparison: I Vitamin D versus placebo (all studies), outcome: I.1 Rate ratio, exacerbations requiring systemic corticosteroids.



Subgroup analyses

Lack of access to individual participant data precluded conduct of prespecified subgroup analyses for the outcome of severe asthma exacerbation according to baseline vitamin D status, asthma severity, concomitant asthma treatment, body mass index, and genetic variation in the vitamin D pathway.

We did not conduct prespecified subgroup analyses for different age groups (children aged less than 5 years versus 5 to 16 years versus adults) due to a lack of severe exacerbations arising in trials that enrolled children. We did not conduct subgroup analyses for different dosing frequencies as some studies combined bolus and daily dosing strategies and could not be classified (Castro 2014; Jensen 2016), and the number of remaining studies within each subcategory was small. We did not perform subgroup analyses for different dose sizes due to the small number of studies and events arising within each subcategory.

All trials investigated effects of vitamin D₃, which precluded the

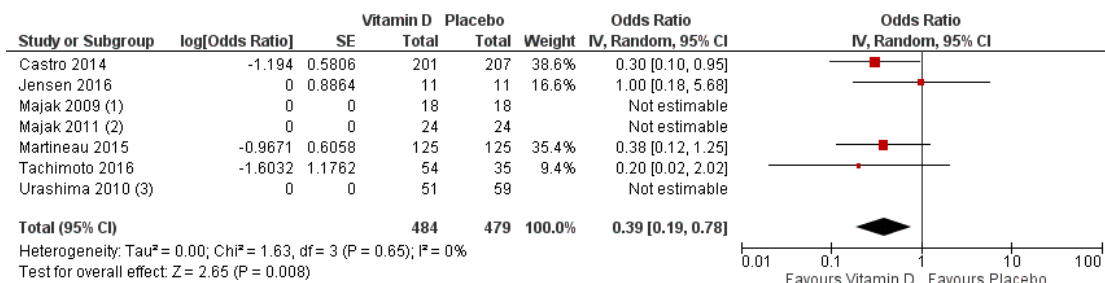
conduct of subgroup analysis by type of vitamin D administered.

Secondary outcomes

Asthma exacerbation precipitating emergency department visit or requiring hospitalisation or both

Administration of vitamin D was associated with a statistically significant reduction in the proportion of participants experiencing an asthma exacerbation precipitating an emergency department visit or hospital admission or both (OR 0.39, 95% CI 0.19 to 0.78; NNTB 27, 95% CI 20 to 76; 963 participants; 7 studies; high-quality evidence; Analysis 1.5; Figure 4). The expected result in 100 people given vitamin D for an average of 7 months is shown in the Cates plot in Figure 5: in comparison with 6 out of 100 with this outcome on placebo, this fell to 3 out of 100 (95% CI 1 to 5) on vitamin D.

Figure 4. Forest plot of comparison: I Vitamin D versus placebo (all studies), outcome: I.5 People with one or more exacerbations requiring ED visit or hospitalisation or both.



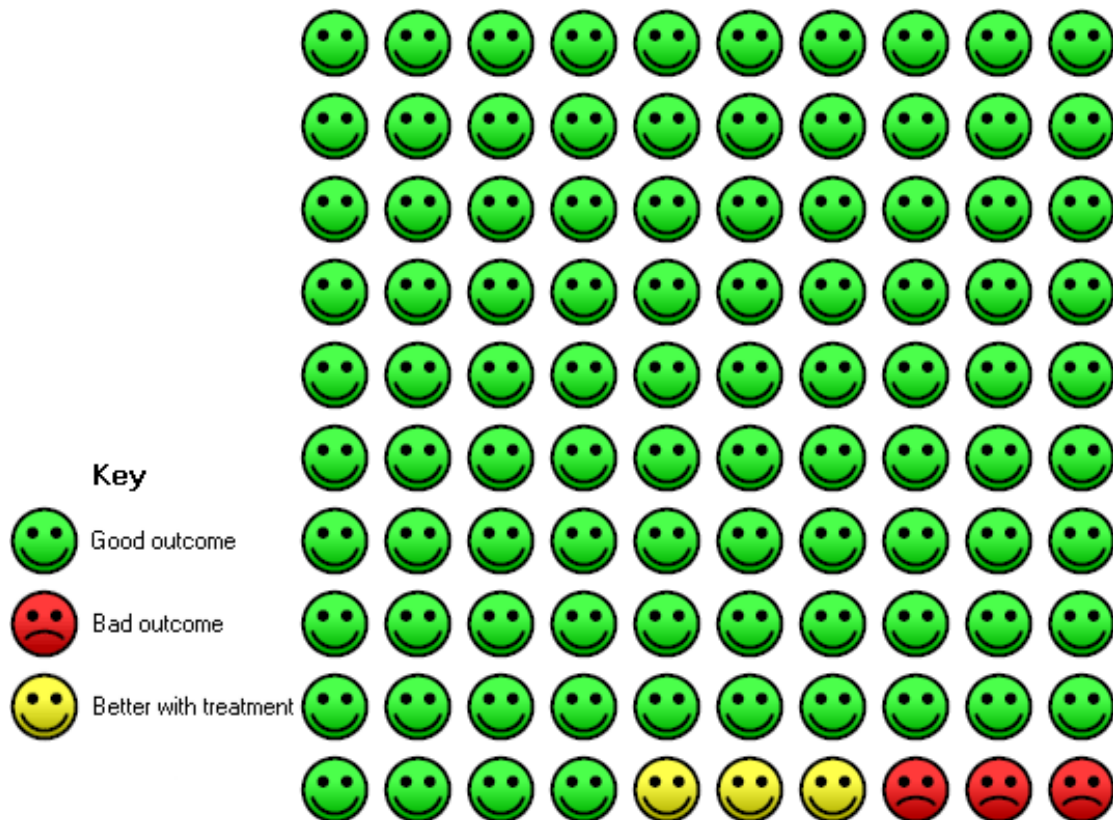
Footnotes

(1) No events in either arm

(2) No events in either arm

(3) No events in either arm

Figure 5. In the control group 6 out of 100 people had a visit to ED or hospitalisation over 8 months, compared to 3 (95% CI 1 to 5) out of 100 on vitamin D.



As only two of the trials conducted in children reported any such events (Jensen 2016; Tachimoto 2016), results of this analysis were primarily driven by the findings of the two trials conducted in adults (Castro 2014; Martineau 2015).

ACT scores

We saw no effect of vitamin D on ACT scores (MD -0.08, 95% CI -0.70 to 0.54; 713 participants; 3 studies; high-quality evidence; Analysis 1.6).

FEV1, % predicted

There was no overall effect of vitamin D on % predicted FEV1 (MD 0.48, 95% CI -0.93 to 1.89; 387 participants; 4 studies; high-quality evidence; Analysis 1.8). We did not include data from one trial that investigated FEV1 as an outcome measure in this meta-analysis because absolute values were reported instead of % predicted values for this study (Castro 2014). Of note, vitamin D did not influence absolute values of FEV1 in this study (change in pre-albuterol FEV1 [L] in intervention vs. control arm over the

course of the study: -0.07 [95% CI -0.14 to 0.01] vs. -0.04 [-0.11 to 0.03], $P = 0.64$).

Serious adverse event, any cause

Administration of vitamin D did not influence the incidence of serious adverse events of any cause (OR 1.01, 95% CI 0.54 to 1.89; 879 participants; 5 studies; $I^2 = 0\%$; moderate-quality evidence; Analysis 1.9)

Fatal asthma exacerbations

No participant in any of the included trials suffered a fatal asthma exacerbation, therefore we saw no effect of the intervention on this outcome (RD 0.00, 95% CI -0.01 to 0.01; 963 participants; 7 studies; $I^2 = 0\%$; low quality evidence; Analysis 1.7).

Asthma exacerbation as defined in primary trial protocols

The definitions of asthma exacerbations used in individual trials are summarised in Table 2. Administration of vitamin D reduced the risk of experiencing at least one such exacerbation (OR 0.53, 95% CI 0.28 to 0.99; NNTB 9, 95% CI 6 to 483; 999 participants; 7 studies; moderate-quality evidence; Figure 6; Analysis 1.10), but there was considerable heterogeneity in study definitions of exacerbation, and I^2 was high (65%). The expected result in 100 people given vitamin D for an average of 8 months is shown in the Cates plot in Figure 7: in comparison with 29 out of 100 with this outcome on placebo, this fell to 18 out of 100 (95% CI 10 to 29) on vitamin D.

Figure 6. Forest plot of comparison: I Vitamin D versus placebo (low risk of bias), outcome: 1.10 People with one or more study-defined exacerbations.

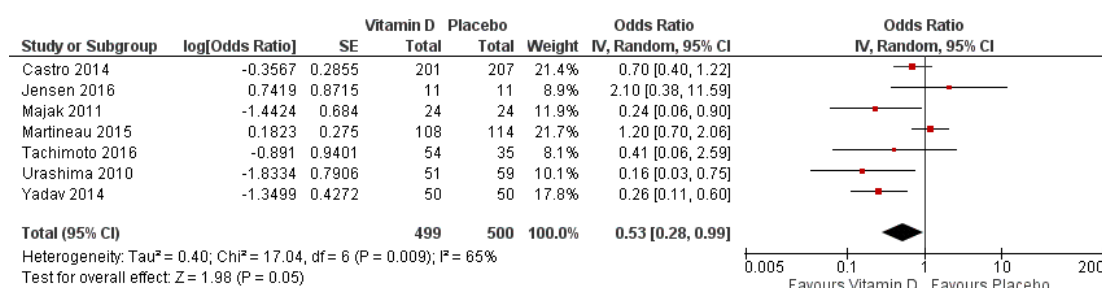
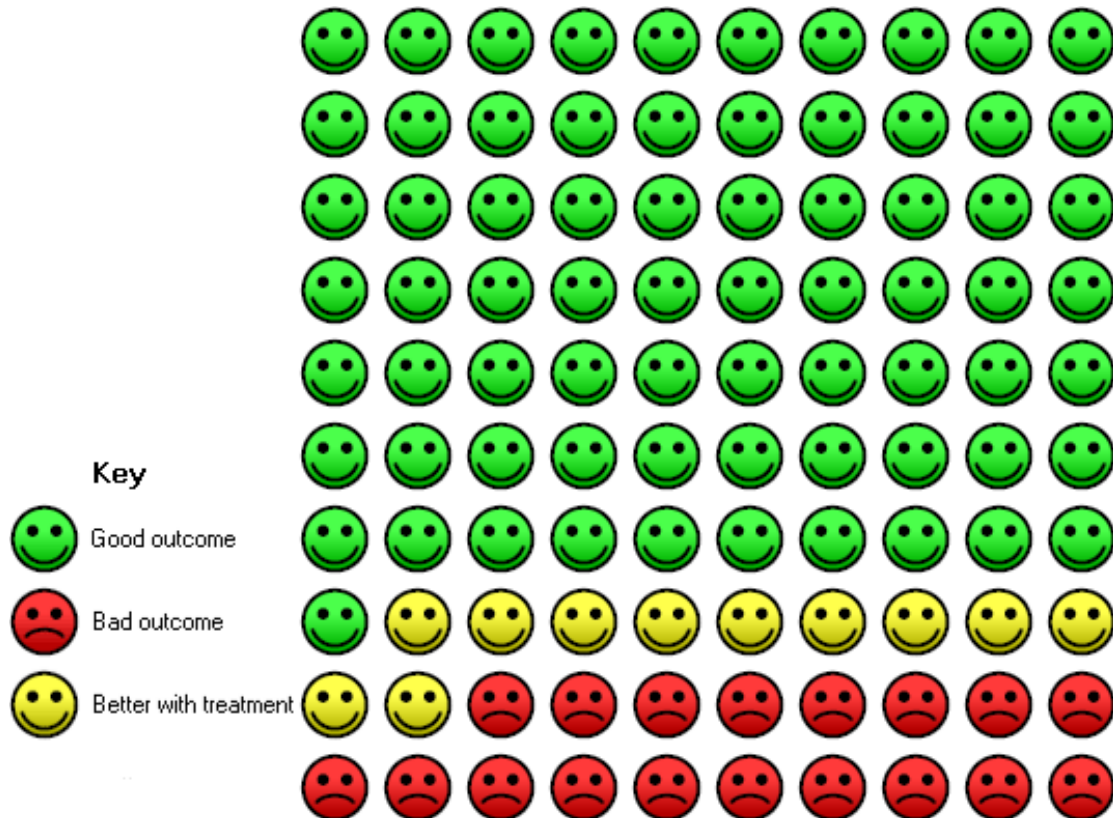


Figure 7. In the control group 29 out of 100 people had a study-defined exacerbation over 7 months, compared to 18 (95% CI 10 to 29) out of 100 on Vitamin D.



Lower airway eosinophilia

Vitamin D did not influence mean eosinophil count in the lower airway (MD -0.38, 95% CI -1.92 to 1.15; 525 participants; 3 studies; high-quality evidence; Analysis 1.11).

Peak expiratory flow rate

Vitamin D did not influence mean end-study peak expiratory flow rate (MD 3.16, 95% CI -13.40 to 19.72; 302 participants; 2 studies; high-quality evidence; Analysis 1.12).

Adverse reaction to vitamin D

Two participants in one trial experienced hypercalciuria ([Jensen 2016](#)), an adverse event that is recognised as an adverse reaction to vitamin D; this event arose in one participant in the intervention arm and one participant in the control arm of a study in which low-dose vitamin D was administered in both arms. No other study reported episodes of hypercalciuria or any other adverse events potentially attributable to administration of vitamin D.

Withdrawals

We saw no difference in the proportion of participants withdrawing from trials between intervention and control arms, but the confidence intervals were wide (OR 1.07, 95% CI 0.73 to 1.58; 1093 participants; 9 studies; moderate-quality evidence; Analysis 1.14).

Time off school or work

One trial conducted in adults investigated the outcome of work absence due to asthma exacerbation or upper respiratory infection ([Martineau 2015](#)). Allocation to vitamin D did not influence such work absence when measured as time to first event (adjusted hazard ratio 0.77, 95% CI 0.53 to 1.10), event rate (adjusted rate ratio 0.86, 95% CI 0.50 to 1.46), or proportion of participants with at least one such absence (adjusted odds ratio 0.77, 95% CI 0.45 to 1.30). No trial conducted in children investigated the outcome of time off school due to asthma symptoms.

Use of inhaled beta2-agonists

One trial conducted in adults investigated the effects of vitamin D on the number of uses of inhaled relief medication per 24 hours (Martineau 2015). Allocation to vitamin D did not influence this outcome at 12 months (adjusted ratio of geometric means 1.00, 95% CI 0.77 to 1.28).

Asthma quality of life

Two trials conducted in adults investigated the effects of vitamin D on respiratory quality of life. Martineau et al reported that administration of vitamin D modestly improved respiratory quality of life as evidenced by adjusted interarm differences in total St George's Respiratory Questionnaire (SGRQ) score of -3.9 points at 2 months ($P = 0.005$), -3.7 points at 6 months ($P = 0.038$), and -3.3 points at 12 months ($P = 0.060$; P for allocation-time interaction = 0.026). These reductions were associated with statistically significant decreases in component scores for the impacts dimension of the SGRQ at two months ($P = 0.05$) and six months ($P = 0.005$; P for allocation-time interaction = 0.030) (Martineau 2015). Of note, the minimum clinically important difference for this score is around 4 points (Jones 2005). Castro et al reported no effect of the intervention on the Asthma Bother Profile score: the adjusted mean change in score was -1.0 (95% CI -2.7 to 0.7) in the intervention arm versus -2.4 (95% CI -4.0 to -0.7) in the placebo arm; $P = 0.16$ (Castro 2014). Data from these two different instruments were unsuitable for pooling and were therefore not meta-analysed.

Fractional exhaled nitric oxide concentration (FeNO)

One trial conducted in adults investigated the effects of vitamin D on FeNO. Martineau et al reported that administration of vitamin D had no effect on mean FeNO concentrations at 12 months (ratio of geometric means -1.4, 95% CI -6.8 to 3.9) (Martineau 2015).

Other immunological biomarkers of asthma control

One trial conducted in adults investigated the effects of vitamin D on concentrations of inflammatory markers in induced sputum supernatants. Martineau et al reported that administration of vitamin D had no effect on supernatant concentrations of a panel of 17 inflammatory markers whose concentrations were detectable, measured at 2 and 12 months (Martineau 2015). Another trial conducted in adults investigated the effects of vitamin D on function of myeloid cells and CD4⁺ T cells in peripheral blood, but found no effect (Castro 2014).

Airway reactivity

One trial conducted in adults investigated the effects of vitamin D on airway reactivity. Castro et al reported that administration

of vitamin D had no effect on the provocative concentration of methacholine at which FEV1 decreased by 20% (PC20): the adjusted mean change in log base 2 transformed PC20 (doubling dilutions) was 0.70 (95% CI 0.38 to 1.03) in the intervention arm versus 0.74 (95% CI 0.41 to 1.07) in the placebo arm; $P = 0.87$ (Castro 2014).

Costs from the perspective of healthcare providers

One trial conducted in adults investigated the effects of vitamin D on health economic outcomes. Martineau et al reported that administration of vitamin D had no effect on total costs associated with asthma/upper respiratory infection over 12 months (adjusted mean difference GBP 66.78, 95% CI GBP -263.47 to GBP 397.03).

Vitamin D versus placebo: sensitivity analysis excluding trials at high risk of bias

Neither of the two trials assessed as being at high risk of bias contributed data relating to incidence of exacerbation treated with systemic corticosteroids or exacerbation precipitating emergency department attendance or hospitalisation or both. One trial assessed as being at high risk of bias reported effects of vitamin D on the proportion of participants experiencing at least one study-defined exacerbation (Yadav 2014). When this trial was excluded in a sensitivity analysis, the effect of vitamin D on this outcome was no longer statistically significant (OR 0.64, 95% CI 0.34 to 1.21; 899 participants; 6 studies; moderate-quality evidence; Analysis 2.1).

Both trials assessed as being at high risk of bias reported effects of vitamin D on the proportion of participants withdrawing from the trial (Lewis 2012; Yadav 2014). When these trials were excluded in a sensitivity analysis, the effect of vitamin D on this outcome remained null (OR 1.17, 95% CI 0.73 to 1.88; 963 participants; 7 studies; $I^2 = 7\%$; moderate-quality evidence; Analysis 2.2).

Vitamin D versus placebo: sensitivity analysis using fixed-effect model

Random-effects and fixed-effect models yielded non-identical but similar results for seven secondary outcomes. Results of analyses performed using each model are presented in Table 1

DISCUSSION

Summary of main results

This systematic review and meta-analysis incorporated evidence from 435 children and 658 adults participating in nine double-

blind, randomised, placebo-controlled trials of vitamin D supplementation; of these, one trial involving 22 children and two trials involving 658 adults contributed to the analysis of the rate of exacerbations requiring systemic corticosteroids. Administration of vitamin D resulted in a clinically and statistically significant reduction in the rate of asthma exacerbations requiring treatment with systemic corticosteroids (RR 0.63, 95% CI 0.45 to 0.88; 680 participants; 3 studies; high-quality evidence; we define a clinically significant reduction in an adverse outcome as being one that patients and clinicians consider large enough to justify a change in treatment). Administration of vitamin D also resulted in a clinically and statistically significant reduction in the risk of asthma exacerbations resulting in emergency department attendance or hospitalisation or both (OR 0.39, 95% CI 0.19 to 0.78; 963 participants; 7 studies; high-quality evidence). Of note, only two of the trials conducted in children reported any severe exacerbations (Jensen 2016; Tachimoto 2016), and both of these trials were relatively small (22 and 89 participants, respectively). Accordingly, results of this analysis were primarily driven by the findings of the two trials conducted in adults (Castro 2014; Martineau 2015). It should also be noted that three out of seven studies for which data on emergency department attendance or hospitalisation or both were available did not report any such events (Majak 2009; Majak 2011; Urashima 2010).

In contrast to the protective effects demonstrated against severe exacerbation, we saw no effect of vitamin D on ACT score (MD -0.08, 95% CI -0.70 to 0.54; 713 participants; 3 studies; high-quality evidence) or % predicted FEV1 (MD 0.48, 95% CI -0.93 to 1.89; 387 participants; 4 studies; high-quality evidence). Vitamin D did not influence the risk of any serious adverse event, although the 95% confidence interval for this outcome was wide (OR 1.01, 95% CI 0.54 to 1.89; 879 participants; 5 studies; $I^2 = 0\%$; moderate-quality evidence). No fatal asthma exacerbations were reported in any trial included in this meta-analysis.

Overall completeness and applicability of evidence

This review incorporated evidence from a relatively modest number of studies, and results should not be generalised to patient populations who are not represented. Specifically, there is a relative lack of evidence on the effects of vitamin D in people with severe asthma, as evidenced by the modest number of exacerbations resulting in emergency department attendance or hospitalisation or both, and the absence of fatal exacerbations. This caveat applies particularly to the studies enrolling children: only 13 of the 305 children included in analysis of the primary outcome experienced an exacerbation that was treated with systemic corticosteroids, as compared with 118 of 628 adults. Consequently, the finding that vitamin D protected against severe asthma exacerbation is based primarily on results of trials conducted in adults, and therefore should not be generalised to paediatric populations. Moreover, the

review does not provide evidence about optimum vitamin D doses and circulating 25(OH)D concentrations.

This review was limited to the inclusion of aggregate data from published manuscripts, which prevented us from conducting any of the subgroup analyses prespecified in the study protocol. Consequently we are unable to comment on whether effects of the intervention are modified by factors such as asthma severity or baseline vitamin D status. Populations with proven profound vitamin D deficiency (serum 25(OH)D less than 25 nmol/L) were also poorly represented in the studies eligible for inclusion in this review; this is particularly significant given that baseline vitamin D status may modify the effects of administering vitamin D on exacerbation risk, a phenomenon that has been reported in people with chronic obstructive pulmonary disease (Lehouck 2012; Martineau 2015a). Conversely, a trend towards increased risk of exacerbation when vitamin D is given to those with higher baseline vitamin D status has been reported (Janssens 2013; Martineau 2015a). Further research to clarify whether baseline vitamin D status modifies effects of vitamin D on exacerbation risk, including individual patient data meta-analysis of existing datasets, is needed before definitive clinical recommendations can be made.

Despite these reservations regarding external validity, there is less reason to doubt the internal validity of our findings: these are based on double-blind, placebo-controlled trials assessed as being at low risk of bias. Moreover, we found effects of vitamin D on risk of exacerbation to be consistent when this outcome was expressed in different ways (RR (Analysis 1.1) versus HR (Analysis 1.2) versus OR (Analysis 1.3)), and when different definitions of exacerbation were used (exacerbations treated with systemic corticosteroids (Analysis 1.1) versus those defined according to study protocols (Analysis 1.10)). For outcomes where vitamin D was found not to have an effect (% predicted FEV1, ACT score), 95% confidence intervals were narrow (Analysis 1.8; Analysis 1.6), effectively ruling out a clinically important effect in the populations studied. The contrast between favourable effects of vitamin D on exacerbation versus null effects of this intervention on other measures of asthma control is striking, and it has implications for choice of outcome measures in future trials. Given that the majority of asthma exacerbations are precipitated by viral upper respiratory infections (Johnston 2006), it seems likely that vitamin D's mechanism of action relates either to prevention of such infections, or to interruption of pathways by which such events trigger exacerbations (Greiller 2015).

Quality of the evidence

This review was restricted to double-blind, placebo-controlled trials; consequently, we assessed all included studies as being at low risk of performance bias and detection bias. We assessed two studies as being at high risk of bias in at least one domain. As neither of these studies contributed data to the primary outcome of this meta-analysis, the evidence contributing to analysis of the effects

of vitamin D on risk of severe asthma exacerbation can be regarded as of high quality. The quality of the evidence relating to adverse event outcomes was lower. Specifically, evidence regarding fatal exacerbations was downgraded two levels to 'low' due to imprecision, as no such events occurred in any included study. Evidence relating to incidence of serious adverse events was downgraded one level due to 'moderate' for imprecision, as confidence intervals for the pertinent odds ratio were relatively wide (0.54 to 1.89).

Potential biases in the review process

We searched multiple databases for eligible studies using prespecified criteria, and this strategy led to identification of unpublished data which are included in this review. As for any review of randomised controlled trials, publication bias may have favoured publication of trials reporting favourable results of vitamin D on asthma outcomes. The total number of studies included in this review is relatively modest, and we identified a further six eligible trials that are ongoing; a repetition of the review in the short to medium term will determine whether or not promising results from meta-analysis of early trials are reinforced by subsequent studies.

Agreements and disagreements with other studies or reviews

We are aware of three other systematic reviews that have synthesised evidence from randomised controlled trials of vitamin D in people with asthma.

The study by Riverin et al (Riverin 2015) included data from eight trials in children, five of which we included in our review (Lewis 2012; Majak 2009; Majak 2011; Urashima 2010; Yadav 2014) and three of which we excluded either on the grounds that they were not placebo controlled (Baris 2014; Darabi 2013), or because duration of follow-up was less than 12 weeks (Schou 2003). Data from Tachimoto et al (Tachimoto 2016), included in this meta-analysis, were not included in Riverin 2015. Riverin 2015 reported a reduction in risk of study-defined asthma exacerbation with vitamin D (RR 0.41, 95% CI 0.27 to 0.63; 378 participants; 3 studies), which was deemed of low quality. No effect of the intervention was seen on asthma symptom scores or lung function. The study by Luo et al included data from seven trials in both children and adults (Luo 2015), four of which we included in our review, and three of which we excluded on the grounds that they did not report asthma control outcomes (Worth 1994), they were not placebo controlled (Baris 2014), or because duration of follow-up was less than 12 weeks (De Groot 2015). Luo et al excluded four studies included in our review (Lewis 2012; Majak 2011; Tachimoto 2016; Urashima 2010). This meta-analysis reported no effect of vitamin D on risk of study-defined asthma exacerbation (RR 0.66, 95% CI 0.32 to 1.37; 820 participants; 3 studies).

The study by Xiao et al focused primarily on effects of vitamin D on risk of acute respiratory infection (Xiao 2015), but it also investigated risk of asthma exacerbation in children as a secondary outcome. This analysis included only two trials (Majak 2011; Urashima 2010), which reported a protective effect of vitamin D against "asthma exacerbation triggered by respiratory infection" (RR 0.28, 95% CI 0.12 to 0.64; 2 studies; n not reported). The findings of our study seem to be in keeping with those of Riverin 2015 and Xiao 2015, but contrast with those of Luo 2015. Disparities in results may be attributable to the inclusion of different primary trials in the different meta-analyses. In addition, the other meta-analyses used heterogeneous definitions of asthma exacerbation, as defined by the primary trial, rather than imposing a universal definition (exacerbation treated with systemic corticosteroids), as we did.

AUTHORS' CONCLUSIONS

Implications for practice

We found a clinically and statistically significant protective effect of vitamin D against severe exacerbation of asthma and no convincing evidence of an increase in serious adverse events. We believe that caution is warranted in applying this evidence to clinical practice because our results come from relatively few trials, none of which has individually reported a statistically significant effect of vitamin D on risk of exacerbation requiring treatment with systemic corticosteroids as a prespecified outcome. Trials predominantly enrolled people with mild or moderate asthma, therefore those with severe asthma are under-represented. Additionally, trials in children made a relatively minor contribution to findings of the review relating to severe exacerbations. Consequently, particular caution should be taken in generalising our findings to people who have recurrent severe asthma exacerbations and to those aged less than 16 years.

Furthermore, it is not yet clear whether beneficial effects of administering vitamin D are experienced by all people with asthma, or whether this result is driven by favourable effects that are confined to particular subgroups (for example those with lower baseline vitamin D status, or frequent exacerbations). Studies in chronic obstructive pulmonary disease have shown a trend towards increased risk of exacerbation when vitamin D is given to those with higher baseline vitamin D status (Janssens 2013; Martineau 2015a). Further research to clarify this issue, including individual patient data meta-analysis of existing datasets, is needed before definitive clinical recommendations can be made.

Implications for research

As discussed above, meta-analysis of individual patient data from the trials included in this review may potentially elucidate clinically

significant subgroup effects. Such a project is ongoing (AVID-Asthma IPDMA), with results expected later in 2016.

We highlight that the optimum vitamin D dose or circulating 25(OH)D level that protects against asthma exacerbations is as yet unknown and requires additional primary studies to determine. There is also a need for new primary randomised controlled trials in populations that are under-represented in the current review, specifically in vitamin D-deficient children and adults who experience recurrent severe exacerbations. Eligibility criteria should be guided by findings of subgroup analyses from individual patient data meta-analysis, which may reveal groups who are more likely to experience benefit or harm from the intervention than others. Our review suggests that such studies are more likely to find effects of vitamin D on exacerbations requiring treatment with systemic corticosteroids than on other outcome measures. These studies should measure participants' vitamin D status both at baseline and at follow-up to allow determination of whether effects of administering vitamin D are dependent on baseline or attained serum 25(OH)D concentrations or both.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Castro 2014

Methods	<p>Randomised, double-blind, placebo-controlled, parallel-group trial</p> <p>Multicentre, 28 weeks long</p> <p>4-week run-in period, prior asthma treatments discontinued</p> <p>48 dropped out from study due to consent withdrawal, treatment failure, and asthma-related adverse event</p> <p>Analysed by intention-to-treat</p>
Participants	<p>9 academic medical centres in the USA, AsthmaNet network</p> <p>Predominantly white/black with some Hispanic and Asian</p> <p>N = 408. 130 m, 278 f. Mean age 39.7 yrs</p> <p>Inclusion criteria:</p> <ol style="list-style-type: none"> 1. 18 years or older with asthma and a serum 25-hydroxyvitamin D level of less than 30 ng/mL. <p>Asthma entry criteria:</p> <ol style="list-style-type: none"> 1. Physician-diagnosed disease. 2. Evidence of either bronchodilator reversibility ($FEV_1 \geq 12\%$ following 180 µg (4 puffs) of levalbuterol) or airway hyper-responsiveness ($PC_{20} \leq 8$ mg/mL). <p>Exclusion criteria:</p> <ol style="list-style-type: none"> 1. Taking vitamin D supplements containing > 1000 IU/day of vitamin D or supplements containing > 2500 mg/day calcium. 2. Chronic oral corticosteroid therapy. 3. Chronic inhaled corticosteroid therapy > 1000 mcg of fluticasone daily or the equivalent. 4. New allergen immunotherapy within the past 3 months. 5. History of physician-diagnosed nephrolithiasis or ureterolithiasis. 6. History of life-threatening asthma within the last 5 years. 7. Use of concomitant medications that alter vitamin D metabolism. 8. Impaired renal function ($GFR < 30$ ml/min) at visit 1. 9. Asthma exacerbation within past 4 weeks requiring systemic corticosteroids. 10. Respiratory tract infection within past 4 weeks. 11. Chronic diseases (other than asthma) that would prevent participation in the trial. 12. History of smoking in the past year. 13. Use of investigative drugs or enrolment in intervention trials in the 30 days prior to screening. 14. Serum calcium greater than 10.2 mg/dl on entry (at visit 1). 15. Urine calcium/creatinine ratio (mg) > 0.37 (at visit 1). 16. More than 8 weeks elapsed between visit 0 (screen) and visit 2 (evaluated at visit 2).
Interventions	<p>Treatment (n = 201): Oral vitamin D₃, 100,000 IU bolus once, then 4,000 IU/day for 28 weeks, added to inhaled ciclesonide (320 µg/d)</p> <p>Control (n = 207): Placebo soft gelatin capsules matching in appearance, added to inhaled ciclesonide (320 µg/d)</p> <p>Median 25(OH)D concentration at baseline: 47 nmol/L. Mean serum 25(OH)D con-</p>

	centration, intervention arm: 105 nmol/L (12 weeks), 107 nmol/L (20 weeks), 105 nmol/L (28 weeks)	
Outcomes	<p>Primary outcome: Time to first asthma treatment failure. Treatment failure defined as 1 or more of the following:</p> <ol style="list-style-type: none">1. peak expiratory flow of 65% or less of baseline measurement on 2 of 3 consecutive measurements.2. FEV1 of 80% or less of baseline measurement on 2 consecutive measurements.3. Increase in levalbuterol dose of 8puffs/d or more for 48 hours (vs baseline).4. Additional use of inhaled corticosteroids or use of oral or parenteral corticosteroids for asthma; emergency department or hospitalisation for asthma with systemic corticosteroid use.5. participant lack of satisfaction with treatment; and physician clinical judgment for safety reasons. <p>Secondary outcomes:</p> <ol style="list-style-type: none">1. Lung function measures. FEV1 (litres and % predicted)2. Asthma symptoms (ASUI)3. Exacerbations4. Asthma-specific quality of life using Asthma Brother Profile5. Impairment from asthma, in terms of productivity loss and activity6. Impairment. Using Work Productivity and Activity Impairment questionnaire (WPAI: Asthma)7. Pharmacogenetics. Potential genetic modifiers of response to corticosteroids and Vitamin D8. Vitamin D levels. Initial and post-randomisation vitamin D levels compared to asthma outcomes.9. Corticosteroid responsiveness. Change in lung function in corticosteroid unresponsive and responsive individuals evaluated. Corticosteroid-responsive airflow obstruction defined as a $\geq 5\%$ improvement in FEV1 following systemic corticosteroids10. Total inhaled corticosteroid dose	
Notes	<p>Grants awarded by the National Heart and Lung Institute. Ciclesonide and levalbuterol were provided without cost by Sunovion Pharmaceuticals Inc The National Institutes of Health (NIH) program officers participated in the design and conduct of the study, and did not participate in the collection, management, analysis, and interpretation of the data The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest</p>	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence

Allocation concealment (selection bias)	Low risk	Study was “double-masked” and active and placebo capsules were matched in appearance. Randomisation code was held by the Data Co-ordinating Centre; the Data Safety Monitoring Board oversaw the trial and reviewed data as the trial progressed in aggregate (group A and B) then unblinded at the end. Allocation was kept concealed until the last participant completed the trial (information from trial report and principal investigator)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind, placebo controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind, placebo controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rates of withdrawal overall, which were seen equally between study arms (17/201 in active arm vs 23/207 in control arm discontinued the study)
Selective reporting (reporting bias)	Low risk	No suggestion of selective outcome reporting; outcomes detailed in Methods were reported in Results. However, we did not have access to the original protocol
Other bias	Low risk	Nil

Jensen 2016

Methods	Single-centre, double-blind, randomised, placebo-controlled trial of 6 months' duration. Concomitant asthma medications were not discontinued during the trial, and analysis was by intention-to-treat. There was no run-in period. The trial was a pilot study, powered to compare the proportion of participants achieving serum 25(OH)D concentration ≥ 75 nmol/L. Target enrolment was 17 per arm, actual enrolment was 11 per arm; enrolment was discontinued on receipt of funding for the substantive trial for which this was the pilot
Participants	Participants (n = 22) were recruited from the asthma clinic, hospital wards, and emergency department of the Sainte-Justine University Health Centre, Montreal, Canada, and randomised to intervention vs control arms of the study in equal numbers. Baseline characteristics were well matched, other than an excess of eczema among participants randomised to vitamin D ₃ vs placebo. Inclusion criteria:

	<ol style="list-style-type: none">1. Age 1 to 5 years.2. Physician-diagnosed asthma, based on clinical signs of airflow obstruction and reversibility.3. URTIs as the main exacerbation trigger, reported by parents.4. ≥ 4 parent-reported URTIs in the past 12 months.5. ≥ 1 exacerbation requiring oral corticosteroids in the past 6 months or ≥ 2 in the past 12 months. <p>Exclusion criteria:</p> <ol style="list-style-type: none">1. Extreme prematurity (< 28 weeks' gestation).2. "High risk of vitamin D deficiency".3. Other chronic respiratory disease.4. Disordered calcium or vitamin D metabolism.5. Oral medications interfering with vitamin D metabolism.6. Vitamin D supplementation greater than 1000 IU/day in the past 3 months.	
Interventions	Active intervention (n = 11): 100,000 IU vitamin D ₃ oral bolus at baseline, followed by 400 IU vitamin D ₃ IU orally daily. Control intervention (n = 11): oral placebo at baseline, followed by 400 vitamin D ₃ IU orally daily. Mean serum 25(OH)D concentration, intervention arm: 62 nmol/L (baseline), 157 nmol/L (10 days)	
Outcomes	<p>Primary outcome:</p> <p>The mean group change in total serum 25(OH)D from baseline to 3 months</p> <p>Secondary outcomes:</p> <ol style="list-style-type: none">1. The proportion of children with total 25(OH)D ≥ 75 nmol/L (30 ng/mL) at 3 months and in total 25(OH)D values over 6 months.2. The proportion of children with hypercalciuria (urinary calcium: creatinine ratio (Ca:Cr) > 1.25 (1 to 2 years) and > 1 (2 to 5 years) mmol/mmol) at any time point.3. Serum calcium, phosphorus, and alkaline phosphatase (ALP).4. Event rates for exacerbations requiring rescue oral corticosteroids (documented in medical or pharmacy records or both).	
Notes	Note that low-dose vitamin D was administered to participants in both intervention and control arms of this trial. Unpublished full text obtained from corresponding author. No conflict of interest identified. Funding: Thrasher Research Fund	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Group assignment, recorded on a sequentially numbered list, was allocated by the Sainte-Justine Hospital Research Pharmacy, which held the randomisation code. To maintain blinding, the intervention and

		placebo dose were identical in colour, appearance, volume, taste, and packaging. All research personnel, physicians, nurses, participants and their parents were blinded to group allocation. The code was not broken until the study trial was complete (information from principal investigator)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind, placebo controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind, placebo controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	21/22 participants were included in analysis of primary outcome
Selective reporting (reporting bias)	Low risk	All prespecified primary and secondary outcomes were reported in the main paper. All exploratory/additional outcomes were also reported, with the exception of the duration of exacerbations and viral infections and the severity of exacerbations (due to poor questionnaire completion rate, as well as space restrictions for the manuscript). The additional outcome of cytokine profile is to be reported separately (information from principal investigator; original study protocol was not obtained)
Other bias	Low risk	Nil. Information on risk of bias for this trial relates to unpublished data

Lewis 2012

Methods	Randomised, double-blind, placebo-controlled, parallel-group trial (pilot study) Single-centre, 12 months long Run-in period not described Concomitant medication: current daily controller asthma medication 10 dropped out of study (reasons not provided) Analysis by intention-to-treat not specified
Participants	Omaha, Nebraska, USA Majority black/Hispanic N = 30, sex distribution not described m/f, age range 6 to 17 yrs Inclusion criteria: 1. Children < 18 years old.

	<p>2. Physician diagnosis of chronic persistent asthma and current daily controller asthma medication.</p> <p>Exclusion criteria:</p> <p>1. Not described.</p>
Interventions	<p>Treatment (n = 15): Oral vitamin D₃, 1000 IU/d for 12 months.</p> <p>Control (n = 15): Placebo (specifications not given) daily for 12 months</p> <p>Study dates not described.</p> <p>Mean serum 25(OH)D concentration, intervention arm: 30 nmol/L (baseline), 68 nmol/L (6 months, summer), 70 nmol/L (12 months, winter). All 25(OH)D concentrations above estimated from figure</p>
Outcomes	<p>Primary outcomes:</p> <ol style="list-style-type: none"> 1. ACT score at baseline, 6 and 12 months. 2. Spirometry (FEV1) at baseline, 6 and 12 months. 3. Serum 25(OH)D levels were measured at baseline, 6 and 12 months. <p>Secondary outcomes:</p> <p>Not given.</p>
Notes	<p>Disclosures: Authors have nothing to disclose.</p> <p>Funding sources: Funding provided by LB595 State of Nebraska Tobacco Settlement funds to Creighton University</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled trial
Incomplete outcome data (attrition bias) All outcomes	High risk	High rates of loss to follow-up (10/30 participants)
Selective reporting (reporting bias)	Low risk	No suggestion of selective outcome reporting: results were reported for outcomes listed as having been investigated in the study report. However, we did not have access to the original protocol

Other bias	Low risk	Nil
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Majak 2009

Methods	<p>Randomised, double-blind, placebo-controlled, parallel-group trial</p> <p>Single-centre, 12 months long</p> <p>Concomitant medication was continued except: inhaled long-acting beta2-agonists, leukotriene modifiers, beta-blockers, multivitamin supplements, and systemic corticosteroids</p> <p>Run-in period: September 2005 to March 2006</p> <p>Analysed on ITT basis</p>
Participants	<p>Lodz, Poland</p> <p>Polish nationals</p> <p>Total N = 54</p> <p>N = 36 used for data extraction, 22 m, 14 f. Age range 6 to 12 yrs</p> <p>Inclusion criteria:</p> <ol style="list-style-type: none"> 1. Children aged 6 to 12 yrs. 2. IgE-dependent asthma with regular symptoms requiring long-term treatment with inhaled corticosteroids. 3. A disease duration of at least 2 years. 4. Sensitised only to house dust mites. <p>Exclusion criteria:</p> <ol style="list-style-type: none"> 1. Poor understanding of a diary used to record daily symptoms. 2. Lack of ability to perform reproducible spirometry, exhibiting the resting FEV1 of at least 70%. 3. No contraindications for SIT. 4. Sensitisation to allergens other than house dust mites. 5. Previously received immunotherapy.
Interventions	<p>Treatment (n = 18): SIT with prednisone 20 mg + oral vitamin D₃, 1000 IU/week for 3 months.</p> <p>Control (n = 18): SIT with prednisone 20 mg + placebo for 3 months</p> <p>SIT with placebo only group (n = 18) was not included as did not allow direct comparison of effect of vitamin D</p> <p>Study dates: April 2006 to April 2007.</p> <p>Mean serum 25(OH)D concentration, intervention arm: 80 nmol/L (baseline), 82 nmol/L (3 months)</p>
Outcomes	<p>Primary outcomes:</p> <p>Inhaled steroid-sparing effect of SIT (dose reduction).</p> <p>Secondary outcomes:</p> <ol style="list-style-type: none"> 1. Clinical outcomes: Asthma symptom score and FEV1. 2. Immunological outcomes: IL-10, TGF-b1, IL-13, IL-5. 3. 25(OH)D.

Majak 2009 (Continued)

Notes	This study was funded by grant 502-12-760 and 503-2056-1 from the Medical University of Lodz, Poland No conflict of interest to declare	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Low risk	Active intervention drugs and placebo were blinded by the hospital pharmacy. The double-blind code was not revealed until the end of the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind, placebo controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Doube blind, placebo controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rates of loss to follow-up, equal between study arms (1/18 for D ₃ + steroid arm vs 1/18 for steroid arm)
Selective reporting (reporting bias)	Low risk	No suggestion of selective outcome reporting: outcomes listed in Methods are reported in Results. However, we did not have access to the trial protocol
Other bias	Low risk	Nil

Majak 2011

Methods	Randomised, double-blind, placebo-controlled, parallel-group trial Single-centre, 6 months long Run-in period: 6 months, concomitant medication discontinued No drop-out, all participants completed follow-up
Participants	Lodz, Poland Mainly Polish nationals N = 48. 32 m, 16 f. Mean age 11.5 yrs, range 5 to 18 yrs Inclusion criteria: 1. Children (5 to 18 yrs) with newly diagnosed asthma. 2. Sensitive only to house dust mites.

	Exclusion criteria: 1. Treatment with an oral, inhaled, or intranasal corticosteroid. 2. Supplementation with vitamin D during the 6 months preceding the trial. 3. History of fractures in the last 2 years. 4. Previous immunotherapy. 5. Obesity (body mass index > 30 kg/m ²). 6. Other chronic diseases.	
Interventions	Treatment (n = 24): budesonide 800 mg daily administered as a dry inhaled powder and oral vitamin D ₃ 500 IU daily. Control (n = 24): budesonide 800 mg daily administered as a dry inhaled powder and oral placebo daily Mean serum 25(OH)D concentration, intervention arm: 90 nmol/L (baseline), 94 nmol/L (6 months)	
Outcomes	Primary outcomes: 1. ATAQ symptom score. 2. Lung function (FEV1). 3. Number of exacerbations. Secondary outcome: Serum vitamin D status at various time points.	
Notes	Supported by grant nos. 502-12-760 and 503-2056-1 from the Medical University of Lodz, Poland. Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind, placebo controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind, placebo controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	100% follow-up
Selective reporting (reporting bias)	Low risk	Nil to suggest selective reporting: results were reported for outcomes listed as having

		been investigated in the study report. However, we did not have access to the original protocol
Other bias	Low risk	Nil

Martineau 2015

Methods	Randomised, double-blind, placebo-controlled, parallel-group trial Multicentre, 12 months long Run-in period: At least 2 weeks, concomitant medication continued 31 did not complete: 17 withdrew consent, 13 lost to follow-up, and 1 died Study analysed on ITT basis
Participants	London, UK Majority (202/250) white British N = 250. 109 m, 141 f. Mean age 47.9 yrs Inclusion criteria: Medical-record diagnosis of asthma treated with ICS. Exclusion criteria: 1. Aged 80 years or above. 2. Tobacco smoking history > 15 pack-years. 3. Medical-record diagnosis of COPD. 4. Failure to exhibit significant variability/reversibility in airway obstruction.
Interventions	Treatment (n = 125): six 2-monthly oral doses of 6 mL Vigantol oil (Merck Serono, Darmstadt, Germany) containing 3 mg (120,000 IU) vitamin D ₃ . Control (n = 125): six 2-monthly oral doses of 6 mL organoleptically identical placebo (Miglyol oil, Caesar & Loretz, Hilden, Germany) Mean serum 25(OH)D concentration, intervention arm: 50 nmol/L (baseline), 61.2 nmol/L (2 months), 69.4 nmol/L (12 months)
Outcomes	Primary outcomes: 1. Time to first severe asthma exacerbation. 2. Time to first URTI. Secondary outcomes: 1. Peak values and areas under the curve for symptom scores during severe exacerbation/URTI. 2. Proportion of days with poor asthma control. 3. Proportion of nights with awakenings due to asthma symptoms. 4. Time to unscheduled healthcare attendance and use of antibiotics for exacerbation/URTI. 5. ACT and SGRQ scores. 6. FeNO concentration. 7. Daily ICS doses. 8. % predicted FEV ₁ , PEF. 9. Use of inhaled relief medication and induced sputum differential cell count and supernatant inflammatory profiles at 2, 6, and 12 months.

	10. Serum concentrations of 25(OH)D and parathyroid hormone (PTH) at 2 months and 12 months. 11. Health economic outcomes (costs of exacerbations and URTI, quality-adjusted life years, and incremental net benefit over 1 year).	
Notes	Funded by the National Institute for Health Research's Programme Grants for Applied Research Programme (ref RP-PG-0407-10398) No competing interests to declare	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Randomisation was performed by manufacturer (Nova Laboratories). Manufacturer and independent data monitoring committee held copies of the randomisation code, which was not revealed to investigators until database lock at the end of the trial. All personnel involved in recruitment and medication delivery were blinded to randomisation (information from trial report and principal investigator)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants contributed data to analysis of co-primary outcomes. Rates of loss to follow-up were comparable between arms (8/125 in intervention arm vs 5/125 control arm)
Selective reporting (reporting bias)	Low risk	Results of all analyses specified in protocol and relating to asthma control are reported; results of analyses relating to symptoms of allergic rhinitis will be reported elsewhere. We had access to the study protocol
Other bias	Low risk	Nil

Tachimoto 2016

Methods	<p>Randomised, double-blind, placebo-controlled, parallel-group trial</p> <p>Multicentre, 6 months long</p> <p>Run-in period: Not described, concomitant medication continued</p> <p>No drop-out, all participants completed follow-up</p> <p>Study analysed on ITT basis</p>
Participants	<p>Tokyo, Japan</p> <p>Predominantly Japanese</p> <p>N = 89. 50 m, 39 f. Mean age 9.9 yrs</p> <p>Inclusion criteria:</p> <ol style="list-style-type: none"> 1. Children aged 6 to 15 years at entry. 2. Diagnosed and treated for asthma by 3 collaborating paediatricians of this trial who were blinded to vitamin D or placebo treatment. 3. Diagnosed according to Global Initiative for Asthma (GINA). <p>Exclusion criteria:</p> <ol style="list-style-type: none"> 1. Already taking a vitamin D supplement. 2. History of hospital admission due to respiratory syncytial virus infection, respiratory treatment by intubation, or urinary tract stone or underlying disease related to calcium or bone. 3. Underlying chronic disease other than asthma including fracture, mental retardation, or swallowing disturbance. 4. Other difficulties judged by the paediatrician in charge.
Interventions	<p>Treatment (n = 54): vitamin D₃ 800 IU/day orally for 2 months.</p> <p>Control (n = 39): daily oral placebo for 2 months.</p> <p>Mean serum 25(OH)D concentration, intervention arm: 71 nmol/L (baseline), 86 nmol/L (2 months), 77 nmol/L (6 months)</p>
Outcomes	<p>Primary outcome:</p> <p>Changes in asthma control levels defined by GINA.</p> <p>Secondary outcomes:</p> <ol style="list-style-type: none"> 1. Assessed changes in asthma control levels judged by the childhood ACT (C-ACT) for children aged 6 to 11 years or the ACT for children aged 12 to 15 years. 2. Changes in Scoring Atopic Dermatitis (SCORAD) between the intervention groups. 3. Subjective visual analog scales of pruritus and sleep loss for the last 3 days or nights, summed by the equation: (Extent/5 + Intensity*7/2 + Visual analog scale). 4. Improvement in pulmonary function: Forced vital capacity % predicted (FVC %), FEV1%, FEV1/FVC ratio (%), and PEFr%. 5. Total IgE and allergen-specific IgE. 6. Serum levels of IL10, IL13, and IL17A.
Notes	<p>This study was supported by the Ministry of Education, Culture, Sports, Science and Technology in the Japan-Supported Program for the Strategic Research Foundation at Private Universities and the Jikei University School of Medicine as well by JSPH KAKENHI Grant Number: 23591553 KAKENHI.</p> <p>All the authors declare no conflicts of interest</p>
<i>Risk of bias</i>	

Tachimoto 2016 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Person performing blinding had no clinical involvement in the trial. Randomisation code was kept by independent data management committee and was not revealed to staff or participants until the trial was complete (information from trial report and principal investigator)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Nil to suggest selective reporting: outcomes listed in Methods are reported in Results. However, the trial protocol was not accessed
Other bias	Low risk	Nil. Information on risk of bias for this trial relates to unpublished data

Urashima 2010

Methods	Randomised, double-blind, placebo-controlled, parallel-group trial Multicentre, 24 weeks long Run-in period: Not described, concomitant medication continued 96 were lost to follow-up, no reasons provided Study analysed on ITT basis
Participants	12 hospitals in Japan N = 430. 242 m, 188 f. Mean age 10.2 yrs, range 6 to 15 yrs Number with diagnosed asthma: 110 Inclusion criteria: 1. Schoolchildren aged 6 to 15 yrs. 2. With or without underlying diseases. Exclusion criteria: 1. Had a history of stones in the urinary tract or diseases of calcium or bone

	metabolism. 2. Was already taking vitamin D ₃ or activated vitamin D as a treatment of an underlying disease. 3. Had a history of allergic reactions to ingredients in the tablets. 4. Had difficulties swallowing tablets. 5. Had been receiving immunosuppressive therapy including oral corticosteroids or chemotherapy within the past year. 6. Were considered incapable of taking part in the study by the paediatrician in charge.	
Interventions	Treatment (n = 217): 3 tablets twice daily (total: 1200 IU vitamin D ₃ /day). Control (n = 213): 3 tablets twice daily (placebo tablets identical in appearance) Those with asthma on treatment n = 51. Those with asthma on placebo n = 59. Vitamin D status not assessed	
Outcomes	Primary outcome: Influenza A, diagnosed by influenza antigen testing. Secondary outcomes: 1. Influenza B diagnosed via nasopharyngeal swab. 2. Physician-diagnosed asthma attack that included wheezing improved by inhalation of a beta-stimulant in children who already had a diagnosis of asthma. 3. Non-specific febrile infection in those who were not suspected to have influenza as well as other specific diseases. 4. Gastroenteritis with 2 of 3 symptoms (nausea or vomiting, diarrhoea, or fever > 37°C). 5. Pneumonia diagnosed with chest X-ray. 6. Admission to the hospital for any reason.	
Notes	Funded by the Jikei University School of Medicine. None of the authors had any conflicts of interest	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Low risk	Allocation was concealed from staff and participants. Randomisation code was kept by independent data management committee and was not revealed to staff or participants until the trial was complete (information from trial report and principal investigator)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Rates of loss comparable between arms for the trial as a whole (50/217 intervention arm, 46/213 control arm), but not reported for subgroup of participants with doctor-diagnosed asthma
Selective reporting (reporting bias)	Low risk	Nil to suggest selective reporting: outcomes listed in Methods are reported in Results. However, the trial protocol was not accessed
Other bias	Low risk	Nil

Yadav 2014

Methods	Randomised, double-blind, placebo-controlled, parallel-group trial Single-centre, 6 months long Run-in period: Not described, concomitant medication continued 18 were lost to follow-up, reasons not provided Study analysed by intention-to-treat
Participants	Rohtak, India Indian N = 100. 49 m, 51 f. Mean age 9.6 yrs, range 5 to 13 yrs Inclusion criteria: 1. Children aged between 3 and 14 yrs. 2. With moderate to severe asthma as per Global Initiative for Asthma (GINA) guidelines, diagnosed by a physician. Exclusion criteria: 1. Children on immunotherapy or anti-IgE. 2. History of premature birth (< 36 weeks). 3. Home use of oxygen. 4. Children with non-wheezy asthma and clinical features of vitamin D deficiency (bony deformities and hypocalcaemic symptoms).
Interventions	Treatment (n = 50): oral vitamin D ₃ (cholecalciferol) 60,000 IU per month for 6 months. Control (n = 50): placebo powder in the form of glucose sachet Vitamin D status not assessed

Outcomes	Primary outcome: Change in the level of asthma severity according to GINA guidelines Secondary outcomes: 1. Number of exacerbations during treatment period. 2. Change in the PEFr. 3. Change in steroid dosage. 4. Level of control. 5. Emergency visits.	
Notes	No details on funding provided. Authors declare no conflict of interest	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not reported
Allocation concealment (selection bias)	Low risk	Allocation concealed in opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled trial
Incomplete outcome data (attrition bias) All outcomes	High risk	10/50 children in control arm and 8/50 in active arm were lost to follow-up, but data for these 'lost' children are presented at the 6-month time point (end of study)
Selective reporting (reporting bias)	Low risk	Nil to suggest selective reporting; outcomes listed in Methods are reported in Results. However, we did not have access to the trial protocol
Other bias	High risk	Marked change in classification of asthma severity between 6-month time point and earlier time points suggests likelihood of misclassification bias operating at end-study time point

25(OH)D, 25-hydroxyvitamin D; ACT, Asthma Control Test; ASUI, Asthma Symptom Utility Index; ATAQ, Asthma Therapy Assessment Questionnaire; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide concentration;

FEV1, forced expiratory volume in one second; GFR, glomerular filtration rate; ICS, inhaled corticosteroids; IgE, immunoglobulin E; ITT, intention to treat; IU, international unit (40 IU vitamin D = 1 microgram vitamin D); PC20, provocative concentration of methacholine at which FEV1 decreased by 20%; PEF, peak expiratory flow rate; SCRG, St George's Respiratory Questionnaire; SIT, specific immunotherapy; URTI, upper respiratory tract infection.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alansari 2015	Not placebo controlled
Arshi 2014	Not placebo controlled
Bantz 2015	Single-blind study
Bar Yoseph 2015	Duration < 12 weeks
Baris 2014	Not placebo controlled
Breitenbuecher 2012	Duration < 12 weeks
Darabi 2013	Not placebo controlled
De Groot 2015	Duration < 12 weeks
Goldring 2013	Primary prevention study
Lakatos 2000	Bone outcomes only
Litonjua 2014	Primary prevention study, protocol only
McDonald 2006	Bone outcomes only
Menon 2014	Not placebo controlled
Nanzer 2014	Duration < 12 weeks
Price 2015	Duration < 12 weeks
Rajanandh 2015	Not placebo controlled
Schou 2003	Duration < 12 weeks
Thijs 2011	Duration < 12 weeks
Torres 2013	Duration < 12 weeks
Utz 1976	Duration < 12 weeks

(Continued)

Worth 1994	Bone outcomes only
Yemelyanov 2001	Bone outcomes only

Characteristics of ongoing studies [ordered by study ID]

NCT01419262

Trial name or title	Vitamin D Outcomes and Interventions In Toddlers
Methods	Double-blind, placebo-controlled RCT
Participants	Children aged 1 to 5 years
Interventions	2000 vs 400 IU vitamin D ₃ orally daily
Outcomes	Upper respiratory infections (primary), asthma exacerbations in subgroup (secondary)
Starting date	September 2011
Contact information	Dr Jonathon Maguire, St Michael's Hospital, Toronto, Canada
Notes	

NCT01728571

Trial name or title	LungVITamin D and Omega-3 Trial
Methods	Double-blind, placebo-controlled RCT
Participants	Adults aged 50 years or older
Interventions	2000 IU vitamin D ₃ orally daily (factorial design with marine omega-3 fatty acids)
Outcomes	Asthma exacerbations and symptoms in subgroup
Starting date	July 2010
Contact information	Prof Diane Gold, Brigham and Women's Hospital, Boston, USA
Notes	

NCT02197702

Trial name or title	Vitamin D in Preschoolers With Viral-induced Asthma (NCT02197702)
Methods	Double-blind, placebo-controlled RCT
Participants	Children aged 1 to 5 years with physician-diagnosed asthma
Interventions	Vitamin D (100,000 IU) given in a 2 ml oral dose at baseline and 3.5 months
Outcomes	Proportion of children with ≥ 1 asthma exacerbation requiring rescue oral corticosteroids
Starting date	September 2014
Contact information	Francine M Ducharme, St Justine's Hospital, Montreal, Canada
Notes	

NCT02424552

Trial name or title	Effect of Vitamin D as add-on Therapy for Vitamin D Insufficient Patients With Severe Asthma
Methods	Double-blind, placebo-controlled RCT
Participants	Adults with physician-diagnosed severe asthma
Interventions	100,000 IU vitamin D ₃ bolus, followed by 4000 IU daily, both orally
Outcomes	Corticosteroid dose (primary), asthma exacerbations (secondary)
Starting date	June 2015
Contact information	Dr Stephanie Korn, Johannes Gutenberg University, Mainz, Germany
Notes	

NCT02428322

Trial name or title	Trial of Vitamin D ₃ Supplementation in Paediatric Asthma
Methods	Double-blind, placebo-controlled RCT
Participants	Children aged 6 to 16 years with physician-diagnosed asthma
Interventions	2000 IU vitamin D ₃ orally daily
Outcomes	Paediatric ACT (primary)
Starting date	October 2013

NCT02428322 (Continued)

Contact information	Dr Basil Elnazir, National Children's Hospital, Dublin, Ireland
Notes	

Patella 2013

Trial name or title	Vitamin D ₃ associated to lactobacillus reuteri improves effects of allergen immunotherapy in asthmatic children
Methods	Double-blind, placebo-controlled RCT
Participants	Children with asthma and house dust mite allergy, age not stated
Interventions	Vitamin D, dose not stated
Outcomes	Asthma symptoms, FeNO, "medication scores"
Starting date	Not reported
Contact information	Prof Vincenzo Patella, Agropoli Hospital, Agropoli, Italy
Notes	Information from published abstract only

UMIN000004160

Trial name or title	A randomized, double blind, comparative study of vitamin D ₃ versus placebo in small children with asthma to prevent asthma attack
Methods	Double-blind, placebo-controlled RCT
Participants	Children aged 2 to 5 years with physician-diagnosed asthma
Interventions	600 IU vitamin D ₃ orally daily
Outcomes	Asthma exacerbations, C-ACT score
Starting date	October 2010
Contact information	Prof Mitsuyoshi Urashima, Jikei University School of Medicine, Tokyo, Japan
Notes	

ACT, Asthma Control Test; C-ACT, Childhood Asthma Control Test; FeNO, fractional exhaled nitric oxide; IU, international unit (40 IU vitamin D = 1 microgram vitamin D); RCT, randomised controlled trial.

DATA AND ANALYSES

Comparison 1. Vitamin D versus placebo (all studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rate ratio, exacerbations requiring systemic corticosteroids	3	680	Rate Ratio (Random, 95% CI)	0.63 [0.45, 0.88]
2 Time to first exacerbation requiring systemic corticosteroids	2	658	Hazard Ratio (Random, 95% CI)	0.69 [0.48, 1.00]
3 People with one or more exacerbations requiring systemic corticosteroids	7	933	Odds Ratio (Random, 95% CI)	0.74 [0.49, 1.10]
4 People with one or more exacerbations requiring systemic corticosteroids (risk difference)	7	933	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.04, 0.02]
5 People with one or more exacerbations requiring ED visit or hospitalisation or both	7	963	Odds Ratio (Random, 95% CI)	0.39 [0.19, 0.78]
6 ACT/C-ACT score	3	713	Mean Difference (Random, 95% CI)	-0.08 [-0.70, 0.54]
7 People with fatal asthma exacerbation	7	963	Risk Difference (M-H, Random, 95% CI)	0.0 [-0.01, 0.01]
8 FEV1, % predicted	4	387	Mean Difference (Random, 95% CI)	0.48 [-0.93, 1.89]
9 People with one or more serious adverse event due to any cause	5	879	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.54, 1.89]
10 People with one or more exacerbation as defined in primary trials	7	999	Odds Ratio (Random, 95% CI)	0.53 [0.28, 0.99]
11 % eosinophils, lower airway	3	525	Mean Difference (Random, 95% CI)	-0.38 [-1.92, 1.15]
12 Peak expiratory flow rate	2	302	Mean Difference (Random, 95% CI)	3.16 [-13.40, 19.72]
13 People with one or more adverse reactions attributed to vitamin D	5	879	Risk Difference (M-H, Random, 95% CI)	0.0 [-0.01, 0.01]
14 People withdrawing from trial	9	1093	Odds Ratio (M-H, Random, 95% CI)	1.07 [0.73, 1.58]

Comparison 2. Vitamin D versus placebo (sensitivity analysis excluding studies at high risk of bias)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 People with one or more study-defined exacerbation	6	899	Odds Ratio (Random, 95% CI)	0.64 [0.34, 1.21]
2 People withdrawing from trial	7	963	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.73, 1.88]

ADDITIONAL TABLES

Table 1. Sensitivity analysis: random-effects versus fixed-effect models

Analysis	Random-effects model	Fixed-effect model
People with 1 or more exacerbations requiring systemic corticosteroids (risk difference)	(RD -0.01, 95% CI -0.04 to 0.02)	(RD -0.03, 95% CI -0.07 to 0.01)
ACT/C-ACT score	(MD -0.08, 95% CI -0.70 to 0.54)	(MD -0.09, 95% CI -0.64 to 0.46)
People with 1 or more serious adverse event due to any cause	(OR 1.01, 95% CI 0.54 to 1.89)	(OR 1.00, 95% CI 0.54 to 1.85)
People with 1 or more study-defined exacerbation	(OR 0.53, 95% CI 0.28 to 0.99)	(OR 0.66, 95% CI 0.48 to 0.91)
% eosinophils, lower airway	(MD -0.38, 95% CI -1.92 to 1.15)	(MD -0.26, 95% CI -1.35 to 0.83)
Peak expiratory flow rate	(MD 3.16, 95% CI -13.40 to 19.72)	(MD 4.09, 95% CI -1.34 to 9.52)
People withdrawing from the trial	(OR 1.07, 95% CI 0.73 to 1.58)	(OR 1.09, 95% CI 0.74 to 1.59)

Sensitivity analyses are presented only for those outcomes where results of analyses using random-effects versus fixed-effect models are non-identical.

Abbreviations: CI, confidence interval; MD, mean difference; OR, odds ratio; RD, risk difference.

Table 2. Definitions of asthma exacerbation used in primary trials

Study	Definition
Castro 2014	Meeting criteria for treatment failure and 1 or more of the following: <ul style="list-style-type: none"> • failure to respond to rescue algorithm within 48 hours; • FEV1 of less than 50% of baseline measurement on 2 consecutive measurements; • FEV1 of less than 40% of predicted level on 2 consecutive measurements; • use of 16 puffs/day or more of as-needed levalbuterol for 48 hours; • experiencing an exacerbation of asthma according to physician opinion;

Table 2. Definitions of asthma exacerbation used in primary trials (Continued)

	<ul style="list-style-type: none"> • use of oral or parenteral corticosteroids due to asthma.
Jensen 2016	Exacerbation requiring rescue oral corticosteroids, documented in medical or pharmacy records or both
Lewis 2012	Exacerbation not defined or reported in study manuscript
Majak 2009	Exacerbation not defined or reported in study manuscript; authors confirmed that no exacerbations requiring systemic corticosteroid treatment occurred in the study
Majak 2011	Reported but not defined in study manuscript; authors confirmed that no exacerbations requiring systemic corticosteroid treatment occurred in the study
Martineau 2015	Deterioration in asthma resulting in (A) treatment with oral corticosteroids, or (B) hospital admission or emergency department treatment, or (C) decrease in the morning PEFR to more than 25% below the mean run-in value on 2 or more consecutive days
Tachimoto 2016	Worsening of asthma symptoms prompting a need for a change in asthma treatment (from authors)
Urashima 2010	Asthma attack that included wheezing, improved by inhalation of a beta-stimulant in participants who already had a diagnosis of asthma; authors confirmed that no exacerbations requiring systemic corticosteroid treatment occurred in the study
Yadav 2014	Reported but not defined in study manuscript

FEV1, forced expiratory volume in one second; PEFR, peak expiratory flow rate.

CONTRIBUTIONS OF AUTHORS

Adrian R Martineau (ARM) and Chris J Griffiths (CJG) wrote the protocol; Christopher J Cates (CJC), Aziz Sheikh (AS), and Ulugbek Nurmatov (UN) commented on it. Mitsuyoshi Urashima (MU) and Megan Jensen (MJ) contributed unpublished data. ARM, Alex P Griffiths (APG), CJC and UN assessed eligibility of trials for inclusion, extracted data, and performed 'Risk of bias' assessments. ARM entered data into Review Manager 5.3 for statistical analysis, which CJC cross-checked. ARM drafted the manuscript, and all review authors critically evaluated it for important intellectual content and gave final approval of the version to be published.

DECLARATIONS OF INTEREST

ARM, MU, MJ, and CJG all acted as investigators in one or more clinical trials contributing data to this review. The 'Risk of bias' assessment for the study authored by ARM and CJG was performed independently by UN and CJC (Martineau 2015). For all other studies, ARM and one of CJC and APG independently assessed the risk of bias for each study. Where data from primary studies conducted by review authors contributed to a given outcome, the quality of the evidence was assessed by review authors who were not involved with those primary studies (CJC and AS).

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol specified that studies published as abstract only would be included, with a note to the effect that they were pending definitive evaluation as and when fuller reports became available ([Martineau 2015b](#)). In conducting the review, where studies were published as abstracts only, we contacted the study authors requesting full text of the trial report. Where this was unavailable, we listed such studies as 'ongoing'.

The protocol specified that exacerbations precipitating emergency department attendance versus hospitalisation would be analysed separately ([Martineau 2015b](#)). However, due to difficulties in differentiating such events, this outcome was pooled in the current analysis.

The protocol did not specify that we would meta-analyse hazard ratios or that we would use generic inverse variance meta-analysis ([Martineau 2015b](#)); however, we employed both techniques in the review.

The protocol did not specify that risk difference would be calculated for some analyses. This was added so that studies where no events occurred could be included.